

**Neglecting the Essentials: Addressing Barriers to Accessing Off-Patent
Essential Medicines for Neglected Diseases in Canada**

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Abstract

In Canada, less than half of the drugs that the World Health Organization classifies as Essential Medicines for the treatment of Neglected Diseases like Chagas disease, drug-resistant tuberculosis, echinococcosis, leishmaniasis, leprosy, malaria and sleeping sickness are formally available, even as collectively hundreds of patients require access to them each year. Essential Medicines, according to the WHO, are those “intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford”. Nevertheless, many of these Essential Medicines, like the conditions they treat, are neglected by pharmaceutical companies and governments alike in low-burden, high-income countries like Canada. The result is a reversal of the usual access to medicines narrative around novel, patented medicines unavailable in low-income countries; these are old, off-patent Essential Medicines, many of which have become widely available in low and middle-income countries yet increasingly difficult to access in many high-income countries. Their absence from countries like Canada is not due to their lack of medical utility – many of them are recognized domestically as the standard of care – but their lack of commercial value. Unfortunately, Canada’s regulatory system is premised upon keeping unsafe, ineffective or poor-quality drugs out, not bringing Essential Medicines in. As a result, these drugs must be accessed through ill-fitting mechanisms like Canada’s Special Access Programme (SAP). Other high-income countries face similar access challenges, though they may manifest in different ways; in the United States for instance, drugs that have disappeared from the Canadian market or simply never been introduced in the first place have instead had *de facto* monopolies unscrupulously exploited. In turn, as the COVID-19 pandemic has served to underscore, access to these Essential Medicines for Neglected Diseases is an issue that cannot be solved solely at the domestic level. Essential Medicines that threaten to disappear before the diseases they treat do also serve to highlight broader issues of domestic and international concern, from drug shortages to antimicrobial resistance. This thesis provides an in-depth exploration of the problem, and offers guidance on what Canada in particular can do about improving access to medicines, especially those for Neglected Diseases that have been largely absent from the Canadian pharmaceutical agenda.

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This thesis is dedicated to SML, for (mostly) putting up with all this.

And in honour of Donald Laughton & C. Stuart Houston, two of the very few people who would have voluntarily read the whole thing.

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Clarification of terms and sources

Before embarking, some minor points of terminology and reference. First, for consistency, this thesis uses the current term Essential Medicines throughout. However, the World Health Organization (WHO) previously used the term Essential Drugs, and as such that term may appear in specific references quoted throughout this thesis. There is ultimately no meaningful difference between these terms.¹ Second, although the term “Essential Medicines” encompasses a broader concept that extends beyond the boundaries of the WHO Model List of Essential Medicines (WHO MEML), any individual drugs referred to by the author as Essential Medicines in this thesis are, unless otherwise specified, found on the 22nd WHO MEML (2021).² Furthermore, except where tradenames affect the narrative or where explicitly noted, this thesis uses the International Nonproprietary Name (INN) for all drugs.

In exploring the availability of Essential Medicines in different countries, this thesis draws heavily from the WHO Model List of Essential Medicines, cross-referenced against the databases of national pharmaceutical regulatory bodies. Unless explicitly noted, information about a drug’s inclusion on the WHO MEML, such as its indications or the year of inclusion, is drawn from the WHO’s Electronic Essential Medicines List (eEML), available online.³ Similarly, unless otherwise stated, information about the market status of drugs in Canada as of April 2022 is drawn from Health Canada’s Drug Product Database, available online; where similar information is drawn from foreign regulators, the equivalent online database for that regulator is used.⁴

¹ As Greene notes, the use of the term essential drugs vs. essential medicines serves simply “to divide historical periods: essential medicines is a twenty-first-century term whereas essential drugs was largely a twentieth-century term”.¹ Greene, Jeremy A. “Making medicines essential: The emergent centrality of pharmaceuticals in global health” (2011) 6:1 BioSocieties 10–33, online: <<http://link.springer.com/10.1057/biosoc.2010.39>>. This shift is in any case an Anglocentric one that belies the universal and continuous nature of the concept; for instance, the term has been “Médicaments essentiels” in French since the first WHO MEML in 1977.

² World Health Organization, *World Health Organization Model List of Essential Medicines – 22nd List, 2021* (Geneva: World Health Organization, 2021) WHO/MHP/HPS/EML/2021.02.

³ World Health Organization, Electronic Essential Medicines List (eEML) online: <<https://list.essentialmeds.org/about>>.

⁴ Health Canada, Drug Product Database, online: <<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>>; see e.g., US Food & Drug Administration, Drugs@FDA: FDA-Approved Drugs online: <<https://www.accessdata.fda.gov/scripts/cder/daf/>>.

Introduction

Prelude

Less than a week into his PhD program, the author received an email from a physician in Edmonton, Alberta, who was searching for insights into a major price hike for cycloserine, a tuberculosis drug vital for caring for patients with multidrug-resistant tuberculosis (MDR-TB).⁵ While only two patients in the province were receiving the drug at the time, the more than twenty-fold increase in its price had raised the total cost of treatment by almost \$30,000CAD per month.⁶ Complicating the matter considerably, this drug, originally developed in the 1950s, was no longer formally available in Canada at all, despite being recognized as a standard of care treatment in Canada's official TB guidelines.⁷ Despite its established medical utility, the pharmaceutical company Eli Lilly – the only company ever to receive market approval for cycloserine in Canada – had made the commercial decision to withdraw it from the Canadian market in 1997.⁸ As a result, despite a long history of use in Canada, the drug could not be purchased through normal channels, but had to be accessed from the United States through the Special Access Programme (SAP), a regulatory bypass mechanism designed for emergency access to novel, unapproved drugs. Attached to the email as background information was a document taken from the website of the Mayo Clinic Center for Tuberculosis in the United States. This short post, entitled "Cycloserine Capsule Price Increase", explained that the Irish pharmaceutical company Rodelis Therapeutics had recently acquired the American rights to market cycloserine, and immediately increased the price from roughly \$500USD to \$10,800 for a blister

⁵ Ryan D. Cooper, Personal Communication (9 Sept. 2021). Cycloserine is also widely known under the proprietary tradename, Seromycin; this issue of tradenames will be revisited.

⁶ Ryan D. Cooper, Personal Communication (9 Sept. 2021).

⁷ Public Health Agency of Canada, *Canadian Tuberculosis Standards*, 7th ed (Ottawa: Minister of Public Works and Government Services, 2014).

⁸ As noted in the clarification of sources, information of this kind is drawn from Health Canada's online Drug Product Database.

pack of 30 tablets.⁹ As a result, the increased costs in Canada, where the drug was not formally available, were simply spillover from the United States, where a monopoly on the production of an old, off-patent medicine was – entirely legally – exploited.

Just over a year later, in the process of finalizing his thesis topic, the author found himself a willing accessory to purchasing albendazole, a decades-old antiparasitic drug, in a country where it was available at an affordable price from the local pharmacy, and importing it into another where it was not formally available at all. The specifics of this incident turn the stereotypical access to medicines story on its head. In the usual version of the tale, people in low and middle-income countries (LMICs) lack access to drugs readily available to Canadians; here, the reverse was true. This purchase was made in Zimbabwe, a low-income country where it is readily available, to be brought back to Canada, where it is not. Although billions of tablets of albendazole have been administered worldwide over the past three decades, it has never been brought to market for human use in Canada, either by the company that invented it – SmithKline, now GlaxoSmithKline (GSK) – or, in the years since its patent expired, makers of a generic version.

Cycloserine and albendazole, like the other drugs that are the focus of this thesis, are considered Essential Medicines by the World Health Organization (WHO). As such, they are found on the WHO's Model List of Essential Medicines (WHO MEML). According to the WHO, Essential Medicines “are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford”.¹⁰ As this thesis illustrates, these criteria were not – and are still not – being met in Canada when it comes to drugs like

⁹ Mayo Clinic Center for Tuberculosis “Update on the Cycloserine Capsule Price Increase” (11 September 2015), online (archived): <https://web.archive.org/web/20151016132525/http://centerfortuberculosis.mayo.edu/the-latest-on-tb/archives/09-2015>.

¹⁰ World Health Organization, “Essential Medicines” (cached 10 January 2021) online: https://web.archive.org/web/20210110015606/https://www.who.int/medicines/services/essmedicines_def/en/.

cycloserine and albendazole. This is despite the fact that there are patients in Canada in need of access to these Essential Medicines, which are considered the standard of care for their indicated condition both domestically and internationally.

A common thread shared by the Essential Medicines discussed in this thesis is that they are used to treat Neglected Diseases: diseases such as malaria, tuberculosis, and the Neglected Tropical Diseases (NTDs). Though evocative, Neglected Disease is not a precisely or universally defined term, in medicine or in law. In his 2007 report on Neglected Diseases, UN Special Rapporteur on the Right to Health Paul Hunt states that the “term ‘neglected diseases’ refers to diseases that continue to burden the poorest of the poor.... They sometimes attract other labels, such as tropical diseases or poverty-related diseases. For the purposes of this report, the term ‘neglected diseases’ is preferred”.¹¹ This thesis shares this terminological preference, as these other labels capture only certain elements of the neglect that unites these diseases. One challenge when looking at Neglected Diseases is that multiple sources have come up with their own set of such conditions.¹² For the purposes of this thesis, “Neglected Disease” will be interpreted broadly and inclusively, drawing from a range of sources, as encompassing infectious diseases that are most prevalent in lower-income countries, and disproportionately effect marginalized populations.¹³

¹¹ Hunt, Paul, ed, *Neglected diseases: a human rights analysis*, Social, economic and behavioural (SEB) research special topics 6 (Geneva: World Health Organization, 2007). Technically, this Special Rapporteur’s full title is Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health.

¹² See e.g., Moran, Mary et al., “Neglected Disease Research and Development: How Much Are We Really Spending?” (2009) 6:2 PLoS Med e1000030, online: <<https://dx.plos.org/10.1371/journal.pmed.1000030>>.

¹³ Four sources were particularly influential in the classification of Neglected Diseases for the purposes of this thesis. The first is the World Health Organization’s list of Neglected Tropical Diseases, online: <<https://www.who.int/news-room/questions-and-answers/item/neglected-tropical-diseases>>. The second is the US FDA’s Current List of Tropical Diseases, listing diseases eligible for the Tropical Disease Priority Review Voucher (PRV) Program, online: <<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program>>. The third is Orphanet’s Inventory of Rare Diseases, online: <<https://www.orpha.net/consor/cgi-bin/Disease.php>>. And the fourth is the page outlining the scope of the journal *PLoS Neglected Tropical Diseases*, online: <<https://journals.plos.org/plosntds/s/journal-information>>. These lists are themselves evolving over time, reflecting the adaptivity of the concept of Neglected Diseases.

In turn, as **Table 1** shows, the number of Essential Medicines listed on the WHO MEML for treating these diseases that are not formally available in Canada is remarkable.

Table 1: Availability of Selected Essential Medicines for Neglected Diseases

WHO MEML Category (22 nd List – 2021)	Number of Essential Medicines per MEML category formally available in Canada (Health Canada Drug Product Database, April 2022)
Intestinal anthelmintics	4/7
Antifilarials	1/3
Antischistosomes and other antitrepatodals	1/3
Antileprosy	2/3
Antituberculosis (drug-resistant TB)	7/15
Antifungals	10/12
Antiamoebic and anti giardiasis	1/3
Antileishmaniasis	2/5
Antimalarials	5/16
African trypanosomiasis (sleeping sickness)	1/6
American trypanosomiasis (Chagas disease)	0/2
Scabicides & pediculicides	1/2

These Neglected Diseases are neglected foremost in that they do not receive the attention they deserve, be it from pharmaceutical companies or governments. That core element of neglect, both of the disease itself and, all too often, the populations affected by it, is present across these diseases. What must be emphasized at this point is that while these diseases are frequently associated with LMICs, they can, and do, affect patients in Canada and other high-income countries (HICs). Some remain endemic even in HICs, often concentrated in marginalized populations; for instance, tuberculosis may be a historical footnote to the average Canadian, but it remains a major public health threat in some communities, particularly Indigenous populations in northern parts of the country. Today, the number of Neglected Diseases clearly recognized as endemic in Canada is relatively small. However, there has been surprisingly little investigation of this question; the neglect of Neglected Diseases means they are a problem that may not always be found unless someone bothers to look. Indeed, even a recent overview of the issue of Neglected Diseases in Canada by high-profile experts managed to completely overlook at least

one clearly endemic condition.¹⁴ Others may not be endemic, but have been regularly imported in an increasingly globalized world; some in turn pose an increasing threat of establishing, or re-establishing, local roots as a result of evolving global conditions like climate change.

Focusing on off-patent Essential Medicines for these Neglected Diseases serves several purposes in this thesis. First, while the term Neglected Diseases was initially coined to draw attention to diseases neglected by pharmaceutical companies and policymakers when it came to developing new treatments, that neglect also extends to ensuring universal, sustainable access to medicines that already exist for these diseases.¹⁵ Moreover, as will be explored, such drugs can become victims of their own success; as a disease becomes less of a public health threat, attention to the disease decreases while the market for drugs to treat that disease becomes less commercially appealing. This problem can manifest at both the national and international levels. Those still affected by a waning disease – often marginalized groups with fewer health resources and less political influence, whether located in LMICs or within HICs like Canada – thus bear the consequences of this combination of political and commercial neglect. In turn, the markets for off-patent Essential Medicines for Neglected Diseases can serve as the canary in the coalmine for broader systemic issues, such as shortages of older medicines in general, or for other crucial issues involving access to medicines, such as

¹⁴ This review by prominent Canadian experts focuses on the twenty diseases currently listed as Neglected Tropical Diseases by the WHO, and concludes that just three are endemic in Canada: echinococcosis, scabies and rabies. As such, it contains at least one bizarre omission. Given that venomous snakes endemic to Canada continue to bite Canadians in Canada, it's unclear why the authors decided to exclude snakebite envenoming from their count. Gyorkos, Theresa W et al., "Canadian contributions to research on neglected tropical diseases" (2021) 15:7 PLoS Negl Trop Dis e0009476, online: <<https://dx.plos.org/10.1371/journal.pntd.0009476>>. Indeed, this is doubly ironic given that snakebite antivenom is another product that can only be obtained via the SAP, even for snakes native to Canada. See e.g., Curran-Sills, Gwynn & Jenna Kroeker, "Venomous Snakebites in Canada: A National Review of Patient Epidemiology and Antivenom Usage" (2018) 29:4 Wilderness Environ Med 437–445.

¹⁵ See e.g., Fürst, Thomas et al. "Global health policy and neglected tropical diseases: Then, now, and in the years to come" (2017) 11:9 PLoS Negl Trop Dis e0005759, online: <<https://dx.plos.org/10.1371/journal.pntd.0005759>>; Smith, James & Emma Michelle Taylor. "MDGs and NTDs: Reshaping the Global Health Agenda" (2013) 7:12 PLoS Negl Trop Dis e2529, online: <<https://dx.plos.org/10.1371/journal.pntd.0002529>>.

antimicrobial resistance (AMR). These are global issues, with global consequences, that also manifest locally in Canada.

At the same time, Essential Medicines for Neglected Diseases also serve to highlight disjuncts in how HICs like Canada address important global health issues at home and abroad. As will be seen, Canada funds programs for mass distribution of albendazole in other countries; it also generously funds a global mechanism that provides affordable access to quality-assured cycloserine. Lack of attention to Neglected Diseases in Canada and other HICs also contrasts with increasing legal and policy interventions targeting another group of diseases that similarly affects small numbers of their citizens: Rare Diseases. In some respects, the Rare Disease and Neglected Disease conversations are reverse images of each other; the quintessential Rare Disease scenario involves lifelong treatment of a genetic disorder with inordinately expensive, novel medicines of sometimes unproven utility, rather than the similarly quintessential cheap, off-patent Essential Medicines whose short-term use to cure Neglected Diseases is well established.¹⁶ At the same time, the two share many aspects in common. In both cases, small market size has historically been a disincentive for pharmaceutical companies to develop new treatments in the first place, let alone to ensure they are formally available on the Canadian market. Often underemphasized is the fact many Rare Diseases are also impacted by lack of access to old, off-patent drugs. And in turn, both kinds of disease frequently depend upon inadequate mechanisms – like Canada’s SAP, discussed *ad nauseum* later on – to access drugs available elsewhere but unapproved in Canada. Rather than siloing these groups of diseases, addressing the barriers to accessing off-patent Essential Medicines for Neglected Diseases would also help to address underlying problems in Canada’s regulatory system. At the same time, while such reforms may have wider implications for a broader spectrum of drugs, it is old Essential Medicines that provide the most obvious entry point.

¹⁶ As will be seen, the reality is more complex.

Focusing on off-patent Essential Medicines for Neglected Diseases also helps draw attention to lower-profile barriers to access.¹⁷ In particular, such a focus sidelines issues of intellectual property (IP), especially patents, that tend to suck up all the oxygen in discussions around access to medicines. The underlying patents on every Essential Medicine for a Neglected Disease highlighted in this thesis expired decades ago. As such, while both more recent patents (such as for new uses or formulations) and other legally sanctioned IP protections such as data exclusivities may impact access in some instances, they are not the fundamental barrier to accessing these drugs. Spotlighting non-IP barriers is important, because treating patents and other IP as the central barrier to access to medicines is at the best of times an oversimplified approach to a complex problem.

The WHO first put forward the formal Essential Medicines concept in 1975, an initiative driven by Director-General Halfdan Mahler.¹⁸ Putting the concept into practice, the first WHO MEML was released in 1977 and contained 208 medicines.¹⁹ Since then, the list has been updated roughly every two years by the WHO Expert Committee on Selection and Use of Essential Medicines. A considerable number of drugs on the inaugural MEML 45 years ago were already decades old; despite advances in pharmaceutical science in the intervening years, quite a few of these drugs, disproportionately including treatments for Neglected Diseases, remain on the MEML today. The list itself has not been static; each revision features additions

¹⁷ There is an extensive literature detailing precisely what “access” itself means, which is beyond the scope of this thesis. However, this author found most influential the model put forward by Frost and Reich in 2008, which comprises four dimensions: architecture, availability, affordability, and adoption. See Frost, Laura J & Michael Reich, *Access: how do good health technologies get to poor people in poor countries?*, Harvard series on population and international health (Cambridge, Mass: Harvard Center for Population and Development Studies : Distributed by Harvard University Press, 2008). For a shorter primer, see Frost, Laura J & Michael R Reich, “Creating Access To Health Technologies In Poor Countries” (2009) 28:4 Health Affairs 962–973, online: <<http://www.healthaffairs.org/doi/10.1377/hlthaff.28.4.962>>.

¹⁸ Mahler, Halfdan. *Prophylactic and Therapeutic Substances : Report by the Director-General*, A28/11 (World Health Organization, 1975).

¹⁹ Bizarrely, even this figure has been contentious. The original list itself contains no official tally, and scholars have come up with widely diverging figures; the author has seen numbers as low as 186 quoted (in Dugani, Sagar, Kishor M Wasan & Niranjana Kissoon. “World Health Organization and Essential Medicines” (2018) 107:5 Journal of Pharmaceutical Sciences 1261–1262, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0022354917308894>>). Rather than attempt a tally himself, the author of this thesis emailed the WHO EML Secretariat, and was told via email on 2 March 2021 that the 1977 list contained 208 medicines.

and deletions, but with a general trend towards the former, with the newest (22nd) MEML containing 479 medicines. However, even today drugs under patent remain a comparatively minor portion of the drugs on the WHO MEML. As of late 2020, only 47 of 458 items on the 21st (2019) edition of the WHO MEML were under patent anywhere in the world.²⁰ An even smaller percentage of those drugs are patented in low-income countries, a long-standing pattern.²¹ This demonstrates that patents are not the key barrier to producing or marketing the vast majority of Essential Medicines, in LMICs and HICs alike. This being the case, the focus on Neglected Diseases highlights a different failure at the core of Canada's drug regulatory system, one echoed in other HICs: that before a drug will be assessed against Canada's regulatory goals of ensuring safety, efficacy and quality, someone has to want to sell it. In the absence of commercial interest, even a drug like cycloserine – an Essential Medicine that was previously sold in Canada and is considered part of the standard of care both in Canada and at the international level – can only be obtained through inefficient, inappropriate mechanisms like the SAP which, as will be explored in detail, has been to the detriment of Canadian patients.

While the primary focus of this thesis is on Canada, access to off-patent Essential Medicines for Neglected Diseases is, as the foregoing suggests, not a solely Canadian issue, nor one that can be resolved entirely within Canada. From the USA to the member states of the European Union, numerous HICs that readily have the resources to meet domestic needs for access to the Essential Medicines under discussion do not currently have formal access to them, nor regulatory systems designed to encourage such access. At times, the same underlying problem of

²⁰ Schultz, Mark & Jaci McDole, *Essential Medicines and Patents: Recent Trends in the Latest Editions of the World Health Organization's Essential Medicines List*, Working Paper (Geneva Network, 2020), online: <https://geneva-network.com/wp-content/uploads/2017/11/Essential-Medicines-and-Patents_02-Dec-2020.pdf>.

²¹ Schultz, Mark & Jaci McDole, *Essential Medicines and Patents: Recent Trends in the Latest Editions of the World Health Organization's Essential Medicines List*, Working Paper (Geneva Network, 2020), online: <https://geneva-network.com/wp-content/uploads/2017/11/Essential-Medicines-and-Patents_02-Dec-2020.pdf>. See also Beall, Reed F, Rosanne Blanchet & Amir Attaran, "In which developing countries are patents on essential medicines being filed?" (2017) 13:1 Global Health 38, online: <<http://globalizationandhealth.biomedcentral.com/articles/10.1186/s12992-017-0262-4>>.

access to off-patent Essential Medicines for Neglected Diseases can manifest in different forms; in turn, what happens in one country can have serious spillover effects in another. For instance, in the United States, with its far larger market, a number of drugs for Neglected Diseases unmarketed in Canada are formally available but have been open to exploitation that affects access in other ways. Consider the cycloserine story that opens this thesis, which is a high-profile example of the trend of off-patent trolling.²² Off-patent trolling – where even in the absence of patents, unscrupulous companies legally obtain the pre-existing marketing and manufacturing rights for important single-source medicines, and use this *de facto* rather than *de jure* monopoly to drastically increase prices – has been the most notorious manifestation over the past few years of the broader problem of ensuring access to off-patent Essential Medicines.²³ It is not the only manifestation, or even the most important, but it has underscored the need to address underlying issues around access to off-patent Essential Medicines, and will be discussed – along with its most notorious proponent, Martin Shkreli, who hit headlines around the world with a massive price hike for the off-patent malaria/toxoplasmosis Essential Medicine pyrimethamine – later in this thesis.²⁴ Under very similar circumstances, the American price hike for cycloserine initiated by an Irish company impacted Canada directly because Canadian physicians were reliant upon the American source of this more than 60-year-old Essential Medicine that was formerly available on the Canadian market and remains recommended in Canadian treatment guidelines to treat a disease that poses a serious public health

²² Houston, Adam R, Reed F Beall & Amir Attaran. “Upstream solutions for price-gouging on critical generic medicines” (2016) 9 J Pharm Policy Pract 15.

²³ Note: While the author and colleagues have previously used the term “generic trolling” elsewhere (e.g., *ibid.*), this thesis opts to use “off-patent trolling”, as the latter more accurately captures the scenario seen with drugs including cycloserine, where the exploited monopoly includes the rights to the original tradename (Seromycin, in the case of cycloserine; in the case of Martin Shkreli and pyrimethamine, Daraprim).

²⁴ Pollack, Andrew, “Drug Goes From \$13.50 a Tablet to \$750, Overnight”, *The New York Times* (20 September 2015), online: <<https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html>>. After more than 60 years on the Canadian market, pyrimethamine was discontinued in 2013 as the result of a commercial decision, even as it remains the standard of care for Canadian patients.

risk. As this example underscores, a problem that transcends national frontiers cannot be examined solely within Canada's borders.

Lastly, like most things in this world, all of the elements at issue in this thesis have been affected by the COVID-19 pandemic. It has been an inescapable public health reminder that Canada does not exist in isolation, whether in terms of disease transmission across borders or of complex global pharmaceutical supply chains. It has simultaneously demonstrated what can be accomplished when adequate resources are dedicated to developing novel pharmaceutical interventions, such as the unprecedented success of COVID-19 vaccine development, and the similarly unprecedented disparities in access that can result when commensurate efforts are not dedicated to ensuring that crucial pharmaceuticals are available to everyone who needs them. More directly, COVID-19 has attracted new attention to old, off-patent Essential Medicines, and to the importance of maintaining access to them. The research for this thesis delved into ivermectin long before it became both a household name and an ideological marker; it is but one of many old Essential Medicines repurposed, to varying utility, in the response to the novel coronavirus. In fact, a disproportionate number of old Essential Medicines plucked from relative obscurity during the pandemic have been for Neglected Diseases, from hydroxychloroquine to artesunate. As will be explored, shortages, or even the complete absence from the market, of Essential Medicines repurposed for the COVID-19 response – whether or not they were actually effective for this newer purpose – have raised questions about numerous aspects of Canada's pharmaceutical system, from domestic production capacity to mechanisms for the importation of products licensed in other jurisdictions. Attempts to address these problems point to potential systemic solutions, and illustrate an increasing willingness on Canada's part to at least consider such solutions. Such solutions are not restricted to off-patent Essential Medicines for Neglected Diseases, but as will be seen, they are at its core.

Canada and Essential Medicines

In 1940, an article entitled “Non-essential Drugs” appeared in the *Canadian Medical Association Journal*.²⁵ It classified drugs into three categories, ranging from “Drugs which are regarded as essential” to “Drugs which are not essential and do not justify importation or manufacture in war-time”. While it did not provide a list of those drugs considered essential, it *did* provide a comprehensive list of drugs deemed *not* essential. A quick perusal of this not-essential medicines list is likely to lead most modern clinicians to agree with their classification (see footnote).²⁶ The article also showcases other themes that will re-emerge in this thesis, from adapting lists of medicines in response to particular circumstances (including a worldwide event disrupting supply chains – in this case, World War II) to Canada taking its lead on pharmaceutical policy from other countries (the same article had been published earlier the same year in *The Lancet* in the United Kingdom).²⁷ In the intervening eight decades, however, Canada itself has never formally adopted a list of those medicines on the other end of the spectrum: Essential Medicines.

The concept of Essential Medicines is at the centre of this thesis. In turn, while the term Essential Medicines is today closely associated with the World Health Organization and the WHO Model List of Essential Medicines, the concept did not simply materialize in a Geneva boardroom one day in the mid-1970s. While the term has been applied in contexts where it has taken on specific medical, ethical and, crucially, legal implications, the concept of Essential Medicines, at its core, rests on an intuitive idea: Some medicines are particularly important for human health. In turn, a simple and effective way to keep track of the most

²⁵ “Non-essential Drugs: Hints to Prescribers” (1940) 43:6 *Can Med Assoc J* 603–604.

²⁶ The list deemed inessential consists of: Glycerophosphoric acid and glycerophosphates, hydrobromic acid, tartaric acid, aconite, balsam of Tolu, Buch leaves, calumba root, Indian hemp, cantharides and cantharidin, cardiazol, caraway seed, cassia bark and fruit, black catechu, cochineal, balsam of copaiba, coriander seed, cubebs, kousso, fig, gelsemium, gentian, hamamelis, jalap, krameria, linseed, lobelia, pelletierine tannate, cream of tartar, psyllium, salicin, salol, scammony, squill, senega, sodium tauroglycocholate, sparteine, strophanthus, tamarind, taraxacum, the oils of pine, almond, camphor, cardamon, caraway, croton, gaultheria and sandal wood, and the following compounds of iron: arsenate, iron and manganese citrate, iron and quinine citrate, iron and potassium tartrate, iron and strychnine citrate, glycerophosphate, hypophosphate, lactate and injection of iron.

²⁷ “Non-Essential Drugs” (1940) 236:6107 *The Lancet* 340.

important drugs is to have a list of them. Such a list can serve not simply as a reference point, but as a springboard for action, not only for medical interventions but for legal ones, and at both the individual and the population level.

Canada's lack of a formal Essential Medicines List (EML) has left it within the minority of the community of nations; according to the WHO, by the early years of the 21st Century, more than 150 countries had an Essential Medicines list.²⁸ At the same time, as the "Model" in "Model List" suggests, the WHO MEML serves as a common reference point for countries to use in developing their own Essential Medicines List, tailored to their own needs and resources. The influence of the WHO MEML goes far beyond simply offering a template, however. The WHO MEML permeates international guidelines for medical treatment. It also influences procurement strategies at both the national and international levels, and underpins a range of authoritative tools that themselves guide international regulatory regimes. As discussed later, access to Essential Medicines has also become widely accepted as a core state obligation under international human rights law.²⁹ Essential Medicines likewise influence other areas of international law, from the international regime for controlled substances to global trade.³⁰

Before exploring such applications, one might also ask why there has been reticence to adopt an EML in Canada thus far. This may partly be a result of misperceptions about the Essential Medicines concept, at least in the form exemplified by the WHO MEML. As will be seen in more detail, such misperceptions include the idea that the WHO MEML is only applicable to LMICs, or that it would

²⁸ Executive Board, World Health Organization, *Revised procedures for updating the WHO Model List of Essential Drugs: a summary of proposals and process*, Executive Board 108th Session Provisional item 4, EB108/INF.DOC./2 (2001).

²⁹ See in particular, UN Committee on Economic, Social and Cultural Rights (CESCR), *General Comment No. 14: The Right to the Highest Attainable Standard of Health (Art. 12 of the International Covenant on Economic, Social and Cultural Rights)*, 11 August 2000, E/C.12/2000/4 at para 43(d).

³⁰ For controlled substances, see e.g., Lohman, Diederik & Damon Barrett, "Scheduling medicines as controlled substances: addressing normative and democratic gaps through human rights-based analysis" (2020) 20:1 BMC Int Health Hum Rights 10; Pettus, Katherine Irene, "Chapter 4 Improving Access to Internationally Controlled Essential Medicines in the Post-UNGASS, Agenda 2030 Framework" in Axel Klein & Blaine Stothard, eds, *Collapse of the Global Order on Drugs: From UNGASS 2016 to Review 2019* (Emerald Publishing Limited, 2018) 85. For trade, there is a voluminous literature to choose from, though often with an emphasis on patents. As a representative example, see Hoen, Ellen 't, "TRIPS, Pharmaceutical Patents and Access to Essential Medicines: Seattle, Doha and Beyond" (2002) 3:1 Chicago Journal of International Law.

restrict access to medicines in HICs. To be clear, the WHO noted the potential utility of Essential Medicines for all countries from the very beginning, dating back to the original 1975 report.³¹ Successful examples of the use of limited lists of drugs in HICs and LMICs alike were similarly highlighted in development of the first WHO MEML in 1977.³² Also from the beginning, some level of explicit recognition of the fact countries possess different levels of resources has always been present within the WHO MEML structure, particularly via the classification of drugs as “core” and “complementary”. Core medicines are those that are efficacious, safe, and cost-effective for priority conditions, based on potential for safe and effective treatment and current and future public-health relevance.³³ The complementary list includes drugs requiring specialized diagnosis, care or training, and thus less suitable for low-resource environments; “in case of doubt”, medicines can also be listed as complementary “on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings”.³⁴ This underscores first of all that the MEML has never been intended to be restricted to low-resource environments, but rather as a universal resource adaptable to different conditions. At the same time, it should be observed that while complementary drugs may not be suitable for low-resource environments, there is no parallel principle suggesting countries that constitute high-resource environments can simply ignore core medicines when they have the resources to make use of them for patients in need.³⁵

Recent years have also seen renewed arguments in favour of the universal applicability of the concept of Essential Medicines. As Magrini and colleagues write,

³¹ Mahler, Halfdan. *Prophylactic and Therapeutic Substances : Report by the Director-General*, A28/11 (World Health Organization, 1975).

³² WHO Expert Committee on the Selection and Use of Essential Medicines, *The selection of essential drugs*, Technical report series / World Health Organization 615 (World Health Organization, 1977) at p. 10.

³³ WHO Expert Committee on the Selection and Use of Essential Medicines, ed., *The selection and use of essential medicines report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children)* (2019).

³⁴ WHO Expert Committee on the Selection and Use of Essential Medicines ed., *The selection and use of essential medicines report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children)* (2019).

³⁵ Here it is worth observing the parallels with human rights arguments, but also the fact that these concepts are not dependent upon human rights concepts.

its “principles and approaches are equally relevant to high-, middle-, and low-income countries and have increasing relevance as countries implement medicines benefits packages as part of universal health coverage”.³⁶ This observation reflects how, at the international level, Essential Medicines have found ever-wider application, including in the global movement towards universal healthcare as a normative goal, manifested most explicitly as part of the Sustainable Development Goals (SDGs).³⁷ Here too, Canada’s failure to adopt or adapt the WHO MEML is not only out of step with international norms, but deprives Canada, and Canadians, of a useful tool with multiple applications.

Despite a lack of official recognition of the WHO MEML or the establishment of a domestic EML, however, the notion of Essential Medicines has long bubbled under the surface in Canada as well. Over a decade before the WHO had formalized the concept, the famed Royal Commission report that helped usher in Canada’s hallowed Medicare system explicitly referred to “the necessity for solutions that enable essential drugs to be readily available and at reasonable cost”.³⁸ It also drew connections between Canada and the rest of the world, including highlighting Canada’s existing recognition of foreign and international standards, including the WHO’s *International Pharmacopoeia*, within its pharmaceutical regulatory regime.³⁹ Half a century later, the Essential Medicines concept has become – in fits and starts – an increasingly prominent component of the drive to at last finish the job of incorporating pharmacare into Canada’s Medicare system. In particular, Essential Medicines were drawn explicitly into the pharmacare discussion in the

³⁶ Magrini, Nicola et al. “Tough decisions on essential medicines in 2015” (2015) 93:4 Bull World Health Organ 283–284.

³⁷ United Nations, *Transforming Our World: The 2030 Agenda for Sustainable Development*, by United Nations, A/RES/70/1 (New York: United Nations, 2015). Goal 3.8 in particular reads “Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all”.

³⁸ Hall, Emmett M (Chair), *Royal Commission on Health Services* (Ottawa: Queen’s Printer, 1964) at p.40. This report is revisited later.

³⁹ Hall, Emmett M (Chair), *Royal Commission on Health Services* (Ottawa: Queen’s Printer, 1964) p.372-373.

context of the 2019 report of the *Advisory Council on the Implementation of National Pharmacare*, commonly known as the Hoskins Report.⁴⁰

The two concepts are a logical fit; after all, when proponents refer to “universal pharmacare”, the “universal” refers to ensuring everyone has coverage, not ensuring access to every conceivable pharmaceutical. Just as some medicines are Essential, others are not Essential but still useful enough to be included within pharmacare, while still others may be determined not to be worthy of coverage, even though not totally bereft of medical utility. Reflecting such gradations, the Hoskins Report suggests that Canada develop not merely one but two lists as part of the process of implementing national pharmacare: A Canadian Essential Medicines List (Canadian EML) and a national formulary. Of these, it is proposed that the Canadian EML be developed first. As revisited in more detail later, this Canadian EML draws explicitly from the WHO MEML. In recommending these two lists, the Hoskins Report demonstrates how an Essential Medicines List is simply one kind of list of medicines with important implications, and that such lists can perform different functions towards achieving the same goal. Particularly crucial here is the differing roles that these two proposed lists would play in the context of Canadian pharmacare; the national formulary would in essence establish a ceiling for coverage, while the Canadian EML would establish a floor.

That said, even as it explicitly references the WHO MEML, the Hoskins Report, like the broader Canadian pharmacare conversation, glosses over the key issue at the heart of this thesis: the fact that some medicines found on the WHO MEML are not formally available in Canada at all. These are not carnival pedlar concoctions; as will be seen, a fair number of them have earned their discoverers the Nobel Prize. While most rational commentators would not consider pharmacare to be a total panacea for all of Canada’s pharmaceutical woes, a focus on pharmacare has nonetheless served at times to obscure other barriers to accessing medicines; it would be doubly ironic if Canada developed its own

⁴⁰ Health Canada, *A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare*. (2019). This report is discussed in detail later.

domestic EML as a building block of pharmacare, without ever addressing the question of drugs on the WHO MEML remaining not merely absent from the Canadian EML or national formulary, but from the Canadian market entirely. In Canada, resource concerns may well factor into the ceiling of the national formulary; they cannot reasonably be used to justify the absence of Essential Medicines recognized as the standard of care from the formal market in the first place. This thesis focuses on the areas where Essential Medicines needed by patients with Neglected Diseases tumble through the cracks, including how the process of developing a Canadian EML might help to fill those gaps at the same time it supports other pharmaceutical initiatives from pharmacare to global health programs.

Lists of medicines and the law throughout history

As the Hoskins Report makes clear, an Essential Medicines List (EML) is not the only kind of medicines list with normative influence or legal implications. Such lists, from formularies to pharmacopeias to EMLs, play different roles; they also impact and overlap with each other.⁴¹ Furthermore, they can exist at different levels, from international lists such as the WHO MEML and the *International Pharmacopoeia* through lists that exist at the level of a country, a province, a private insurance provider, or even a particular health facility.⁴² Such interrelated lists can have ramifications in areas from regulatory standards to enforceable human rights obligations. These impacts can be direct, ranging from establishing explicit state obligations or patient entitlements, to setting certain legal standards for quality that must be met by producers of a drug. They may also be indirect, such

⁴¹ Perhaps surprisingly, especially given the frequent legal ramifications of such lists, there remains no universal consensus on the precise difference between a pharmacopoeia and a formulary. In very broad strokes, a pharmacopoeia generally functions more like a recipe book for drugs, providing information on their preparation. A formulary functions more like a menu for what drugs are actually available; availability may refer to physical availability (e.g., what should be stocked in a hospital) or financial reimbursement (i.e., a list of reimbursable drugs under an insurance plan). In practice, however, the line between these two terms is often blurred, making it unwise to depend solely upon the label used rather than the contents of the specific list in question. Both kinds of list can be used on their own, in tandem, or in relation to an EML.

⁴² For the most recent version of the International Pharmacopoeia, see World Health Organization, *International Pharmacopoeia*, 9th ed. (2019), online: <<https://apps.who.int/phint/2019/index.html#d/b.1>>.

as outlining a relevant standard of patient care that can be used as a point of reference in relation to a legal duty owed by clinicians or others.

Indeed, standardized compendia of medicines used for some or all of these purposes go back thousands of years and have been employed across multiple medical traditions. The basic concept can be traced at least as far as ancient Egypt, with documents like the Ebers Papyrus surviving from the 16th Century B.C., and thought to include remedies dating from far older works.⁴³ In turn, such reference works could be highly influential across borders; for instance, *De materia medica*, originally written around the year 50 A.D. by the Greek physician Pedanius Dioscorides, would impact medical practice throughout both Europe and the Islamic world for hundreds of years.⁴⁴ In Europe, the emergence of the concept of an official pharmacopoeia with legal implications has been associated with the Salerno Medical Edict of Fredrick II of Sicily in 1240.⁴⁵ However, pharmacopoeias in the modern sense would not emerge in Europe until closer to the 16th Century.⁴⁶ This was accompanied by other efforts at pharmaceutical regulation. In England, for example, manufacturers of medicines were subjected to supervision under the *Apothecaries Wares, Drugs and Stuffs Act* in 1540; this law included the appointment of inspectors, and could be seen as an early example of formal

⁴³ See e.g., Major, Ralph H, "The Papyrus Ebers" (1930) 2:5 Ann Med Hist 547–555.

⁴⁴ See e.g., De Vos, Paula, "European materia medica in historical texts: longevity of a tradition and implications for future use" (2010) 132:1 J Ethnopharmacol 28–47. For impact in the Islamic world in particular, see Vedat Yildirim, Rifat, "Studies on De Materia Medica of Dioscorides in the Islamic era" (2013) 65:1 Asclepio p007, online: <<http://asclepio.revistas.csic.es/index.php/asclepio/article/view/542/556>>.

⁴⁵ The edict drew regulatory distinctions between physicians and apothecaries, and ordered apothecaries to always prepare remedies in the same way. Penn, R G, "The state control of medicines: the first 3000 years" (1979) 8:4 Br J Clin Pharmacol 293–305; see also Kopp, Sabine & Lembit Rago. "The International Pharmacopoeia in the changing environment" (2007) 9:3–4 Pharmaceuticals, Policy and Law 357–368 at p.357. While beyond the scope of this thesis, it's worth noting that such lists of drugs and their preparation also historically underpin regulation in the Islamic world during the Middle Ages; as a widely-cited starting point for this interesting area, see Levey, M, "Fourteenth century Muslim medicine and the Hisba" (1963) 7 Med Hist 176–182.

⁴⁶ The "first official pharmacopoeia in Europe in the modern sense" has been identified by some as the *Nuovo receptario composto dal famosissimo Chollegio degli eximii Doctori della Arte et Medicina della inclita cipta di Firenze*, issued in Florence in 1498. Penn, R G, "The state control of medicines: the first 3000 years" (1979) 8:4 Br J Clin Pharmacol 293–305. Others have suggested that the *Dispensatorium Pharmacorum Omnium*, issued in 1546 with the sanction of the Senate of Nuremberg, was the first volume on drugs "with the imprint of authority". Dunlop, D M & T C Denston, "The History and Development of the 'British Pharmacopoeia'" (1958) 2:5107 BMJ 1250–1252, online: <<https://www.bmj.com/lookup/doi/10.1136/bmj.2.5107.1250>>.

inspection of drug production facilities.⁴⁷ By 1618, King James I would issue a proclamation requiring all apothecaries of the realm of England to follow the just-released *Pharmacopoeia Londinensis* (London Pharmacopoeia).⁴⁸ Even William Shakespeare made reference to the laws governing pharmaceuticals and their makers in Europe. When lovesick Romeo requests “a dram of poison”, the apothecary initially responds, “Such mortal drugs I have, but Mantua’s law/Is death to any he that utters them.”⁴⁹ This line would be cited by Justice Dickson of the Supreme Court of Canada in his dissent in *R. v. Wetmore*, a case whose significance for Canadian pharmaceutical law is touched upon elsewhere in this thesis.⁵⁰

Such developments occurred despite the very primitive state of medical science at the time; the evolution of lists of drugs, both nationally and ultimately internationally, would be further impacted by the evolution of pharmaceuticals themselves, from dubious concoctions rooted in tradition or even magic to truly effective, and in some cases Essential, medicines.⁵¹ In the 18th Century, the apothecary’s pharmacopoeia might have included a few effective natural remedies that form the basis for drugs that would become Essential Medicines, such as cinchona bark for malaria, or opium for pain. It was only by the early 19th Century, however, that the active ingredients of these remedies – quinine and morphine, respectively – had been isolated.⁵² The first synthetic drug to come into widespread use (chloral hydrate, a sedative/hypnotic) did not do so until the final third of the 19th Century.⁵³ The first synthesized Essential Medicine (acetylsalicylic acid) only

⁴⁷ Kopp, Sabine & Lembit Rago. “The International Pharmacopoeia in the changing environment” (2007) 9:3–4 *Pharmaceuticals, Policy and Law* 357–368. At 357.

⁴⁸ King James I, *By the King. A proclamation commanding all apothecaries of this realme, to followv the dispensatory lately compiled by the Colledge of Physitions of London* (26 April 1618).

⁴⁹ Shakespeare, William. *Romeo & Juliet* (Act V, Scene I). In *The complete works of William Shakespeare*. (New York: Gramercy Books, 1997).

⁵⁰ *R. v. Wetmore*, [1983] 2 S.C.R. 284 at p.295.

⁵¹ Dunlop and Denston describe many of the inclusions in the original London Pharmacopoeia of 1618 as being of “bizarre and even revolting character”. Dunlop, D M & T C Denston, “The History and Development of the ‘British Pharmacopoeia’” (1958) 2:5107 *BMJ* 1250–1252, online: <<https://www.bmj.com/lookup/doi/10.1136/bmj.2.5107.1250>>.

⁵² Huxtable, R J & S K Schwarz, “The isolation of morphine – first principles in science and ethics” (2001) 1:4 *Mol Interv* 189–191.

⁵³ Jones, Alan Wayne, “Early drug discovery and the rise of pharmaceutical chemistry” (2011) 3:6 *Drug Test Anal* 337–344.

hit the market, under the tradename Aspirin, in the last years of that century.⁵⁴ It was during this period of scientific advancement that, as will be explored in more detail later on, domestic pharmaceutical regulation began to take a more modern form. As will be seen, however, even as lists of medicines have consistently demonstrated their utility in regulating pharmaceuticals, advances in tackling different diseases have not always occurred at the same pace.

In turn, as both pharmaceutical science and international law evolved in the 19th and early 20th Centuries, the world came very close to establishing not only an international reference list of medicines, but a legally binding one. This was on the cusp of coming to pass in the years following the Second World War, only to falter at the last minute and leave the world with the *International Pharmacopoeia*, which exerts legal influence but remains non-binding on its own. Efforts to develop such a global instrument long predate the WHO itself. According to Miller, the “date when pharmacists first dreamed of an international pharmacopeia is lost to history, but as early as 1865 discussions of it began to appear on the agenda of international pharmaceutical and medical congresses”.⁵⁵ Kopp and Rago highlight the importance of discussions held in 1874.⁵⁶ The first international conference on this matter, convened by Belgium in 1902, led to the first binding multilateral legal instrument, the *Agreement for the Unification of the Formulae of Potent Drugs*, ratified by 19 countries in 1906.⁵⁷ This was followed in the wake of the First World War by the *Agreement Revising the Agreement Respecting the Unification of Pharmacopoeial Formulas for Potent Drugs* (often referred to as the Brussels Agreement), which was drawn up in 1925 and ratified in 1929 under the auspices

⁵⁴ As an intriguing aside, both Aspirin and Heroin – each originally a tradename – were developed and brought to market by Bayer at almost the same time. Sneader, Walter, “The discovery of heroin” (1998) 352:9141 *The Lancet* 1697–1699, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673698071153>>.

⁵⁵ Miller, Lloyd C. “An International Pharmacopoeia” (1953) 8:5 *Food & Drug LJ* 293.

⁵⁶ Kopp, Sabine & Lembit Rago. “The International Pharmacopoeia in the changing environment” (2007) 9:3–4 *Pharmaceuticals, Policy and Law* 357–368.

⁵⁷ *Agreement for the Unification of the Formulae of Potent Drugs* (1906). See also Kopp, Sabine & Lembit Rago. “The International Pharmacopoeia in the changing environment” (2007) 9:3–4 *Pharmaceuticals, Policy and Law* 357–368.

of the League of Nations.⁵⁸ In turn, a technical commission formed by the League in the 1930s would ultimately serve to bridge the transition to the WHO when the technical commission's report was published after WWII.⁵⁹ Its postwar publication was met favourably; hailing it, a brief note in *The Lancet* remarked that the "healing art of Hippocrates may recognise no distinction of race or nationality, but the reluctance of civilised man to depart from medieval standards of sovereignty still denies the world an international pharmacopoeia".⁶⁰

The newly formed WHO seemed well poised to deliver. Indeed, the Organization seemed purposefully designed to create a legally binding tool for standardizing pharmaceuticals. Article 21 of the WHO Constitution outlines the regulatory power of the WHO, and the limited list of subject matter it may apply to; Art.21(d) explicitly grants the authority to "issue standards with respect to the safety, purity and potency of biological, pharmaceutical and similar products moving in international commerce".⁶¹ Per Article 22, such regulations become binding on all WHO members who do not actively reject them.⁶² As such, formulating requirements along these lines for pharmaceuticals as a binding document with near-universal application would have appeared to be a simple matter. To this end, the WHO's Expert Committee on Unification of Pharmacopoeias was formally established by the World Health Assembly (WHA) in 1948.⁶³ Even before the explicit formalization of the Committee, it was recognized that the focus of such a list would be on drugs that were "essential"; medicines for diseases like tuberculosis were explicitly cited as examples.⁶⁴

⁵⁸ *Agreement Revising the Agreement Respecting the Unification of Pharmacopoeial Formulas for Potent Drugs* (1929).

⁵⁹ Technical Commission of Pharmacopoeial Experts, "The Unification of Pharmacopoeias. Interim Report of the Technical Commission of Pharmacopoeial Experts" (1946) 71:847 online: <<http://xlink.rsc.org/?DOI=an946710494b>>.

⁶⁰ "An International Pharmacopoeia" (1946) 247:6403 *The Lancet* 745–746, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673646905417>>.

⁶¹ Constitution of the World Health Organization (1946), Art. 21(d).

⁶² Constitution of the World Health Organization (1946), Art 22.

⁶³ In 1951, this became the Expert Committee on the International Pharmacopoeia, and subsequently in 1959, the Expert Committee on Specifications for Pharmaceutical Preparations.

⁶⁴ "Expert Committee on the Unification of Pharmacopoeias Report on the First Session, Held 13-17 October 1947, Palais des Nations, Geneva (presented to the Interim Commission at its fourth

By the early 1950s, the WHO was on the brink of producing a legally binding instrument. In 1951, the Executive Board of the WHO adopted a resolution that invited the Director-General to “prepare regulations, to be adopted in accordance with Article 21 (D) of the Constitution of the World Health Organization, in which the International Pharmacopoeia would be embodied and which would replace the 1929 Brussels Agreement”.⁶⁵ These proposed regulations would have established a binding regulatory instrument. However, the Executive Board’s approach had shifted by the following year, when it adopted a resolution that would advance the repeal, but not the replacement, of the *Brussels Agreement*.⁶⁶ This would prove to be what came to pass.⁶⁷ It is unclear precisely what occurred to shift the Executive Board’s position; proceedings from an Executive Board session in early 1952 suggest the original repeal-and-replace provision “proved very difficult from the legal point of view, and on the advice of the Legal Office the Expert Committee agreed to having the Agreement terminated by a protocol”, but there is no explanation why regulations under Art. 21(d) would not come into effect subsequently.⁶⁸ That said, it appears some countries like the United States evidently felt the resulting *International Pharmacopoeia* still went too far even in its non-binding form, suggesting they may have influenced the decision not to implement binding regulations.⁶⁹ Whatever the case, as Miller stated at the time, “the net result is that there is now no binding international agreement in the area”.⁷⁰ He concluded that how long this “situation will prevail is for the future to determine”; close to 70 years later, there are still no binding regulations relating to

session)” (November 1947) WHO.IC/127; Chisholm, B. “The World Health Organization” (1950) 1:4661 BMJ 1021–1027, online: <<http://www.bmj.com/cgi/doi/10.1136/bmj.1.4661.1021>>.

⁶⁵ Executive Board. (1951). The International Pharmacopoeia and the Brussels Agreement of 1929. World Health Organization. EB8.R40 online: <<https://apps.who.int/iris/handle/10665/86918>>.

⁶⁶ Executive Board. (1952). Protocol to terminate the Brussels Agreement of 1906 and 1929. World Health Organization EB9.R95. online: <<https://apps.who.int/iris/handle/10665/86918>>.

⁶⁷ *Protocol for the Termination of the Brussels Agreements for the Unification of Pharmacopoeial Formulas for Potent Drug and final act of the meeting of the governments parties to the said Brussels agreements* (1952).

⁶⁸ Executive Board, World Health Organization, *Expert Committee on the International Pharmacopoeia: Report of the Ninth Session*, EB9/74 (1952).

⁶⁹ See e.g., Horan, John J. “A WHO International Pharmacopoeia” (1953) 8:10 Food & Drug LJ 656.

⁷⁰ Miller, Lloyd C. “An International Pharmacopoeia” (1953) 8:5 Food & Drug LJ 293.

the *International Pharmacopoeia*.⁷¹ Subsequent WHO lists of drugs, like the Model List of Essential Medicines, would find themselves in a similar grey area when it comes to their direct legal ramifications, even as they have asserted considerable legal influence. It is within this grey area that much of this story takes place.

Arsenic and old drugs

Before delving into the present-day situation in more detail, it is worth considering how Essential Medicines for Neglected Diseases came to exist in the first place. In considering what an Essential Medicine is, it is also helpful to clarify what an Essential Medicine is not. An Essential Medicine is not, to be clear from the outset, a perfect medicine. It may be a wonder drug, but often it will not be; in fact, there are numerous Essential Medicines found on the WHO MEML that are far from ideal. Even a Nobel Prize, something sprinkled liberally throughout these pages, does not signify perfection. Some Essential Medicines are only moderately effective, while others have side effects ranging from the deeply unpleasant to the potentially deadly. What makes them Essential Medicines is that they fill an important gap in treatment that would otherwise be unfilled.

The imperfect nature of many existing Essential Medicines becomes particularly evident when it comes to the treatment of Neglected Diseases. Neglected Diseases are already widely cited as the classic illustration of market failure in the pharmaceutical industry when it comes to innovation.⁷² For many Neglected Diseases, the total number of people infected or affected worldwide is large; the “small markets” that foster neglect of R&D in this area are measured in terms of dollar value rather than prospective patients or public health impact. In such situations, drugs that are vitally needed – so-called “missing medicines” – may never even be developed in the first place.⁷³ This is a longstanding problem. Trouiller & Olliaro found that of the 1223 new chemical entities commercialized

⁷¹ Miller, Lloyd C. “An International Pharmacopoeia” (1953) 8:5 Food & Drug LJ 293.

⁷² See e.g., Trouiller, Patrice et al., “Drugs for neglected diseases: a failure of the market and a public health failure?” (2001) 6:11 Trop Med Int Health 945–951, online: <<http://doi.wiley.com/10.1046/j.1365-3156.2001.00803.x>>.

⁷³ Wirtz, Veronika J et al. “Essential medicines for universal health coverage” (2017) 389:10067 *The Lancet* 403–476, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673616315999>>.

worldwide between 1975 (the year the WHO formally introduced the Essential Medicines concept) and 1996, only 13 were intended for tropical diseases.⁷⁴ Of this already paltry tally, few were the results of targeted research by pharmaceutical companies, with most coming from government or academic institutions, or being repurposed from veterinary research.⁷⁵ A follow-up study found that of the 336 new chemical entities approved from 2000 to 2011, only four – three of them for malaria – were approved for Neglected Diseases.⁷⁶ Little has changed since. This lack of interest in developing novel treatments has a further consequence however, one that receives less attention. It means that whatever treatment currently exists for a given Neglected Disease may be an Essential Medicine by default, whatever its flaws.

The definitive example of an Essential Medicine as imperfect as it is Essential is melarsoprol, which has been included on the WHO MEML since the inaugural list in 1977. It is used to treat African trypanosomiasis (sleeping sickness), one of the archetypal Neglected Diseases. Indeed, where attempts have been made to further subdivide Neglected Diseases into “neglected” and “most neglected”, sleeping sickness falls squarely into the latter category.⁷⁷ This parasitic

⁷⁴ This article predates the popularization of the terms Neglected Diseases and Neglected Tropical Diseases; here the term tropical diseases covers similar ground. Trouiller, P & P L Olliaro, “Drug development output from 1975 to 1996: what proportion for tropical diseases?” (1998) 3:2 Int J Infect Dis 61–63.

⁷⁵ Trouiller, P et al. “Is orphan drug status beneficial to tropical disease control? Comparison of the American and future European orphan drug acts” (1999) 4:6 Tropical Medicine & International Health 412–420, online: <<https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-3156.1999.00420.x>>.

⁷⁶ Pedrique, Belen et al., “The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment” (2013) 1:6 Lancet Glob Health e371–379.

⁷⁷ In such a subdivision, malaria and tuberculosis would fall into the former category; other conditions like Chagas disease would be found in the latter. Redfield, Peter. “Doctors Without Borders and the Moral Economy of Pharmaceuticals” in Alice Bullard, ed, *Human Rights in Crisis*, 1st ed (Routledge, 2008) at p. 129. Similar classifications would include Type II (neglected) and Type III (very neglected) diseases as outlined in Sachs, Jeffrey & World Health Organization, eds, *Macroeconomics and health: investing in health for economic development; report of the Commission on Macroeconomics and Health* (Geneva: World Health Organization, 2001). A subsequent attempt to quantify these latter categories would directly contrast their burden in LMICs and HICs, with Type II having a burden 3 to 35 times higher in LMICs and Type III a burden greater than 35 times higher. Kindhauser, Mary Kay & World Health Organization, *Communicable diseases 2002: global defence against the infectious disease threat* (Geneva: World Health Organization, 2003). In this author’s view, it is unfortunate that this system of classification never attracted more attention, as it better

disease, along with the tsetse fly that serves as its vector, is found only in certain parts of sub-Saharan Africa. There are two forms of the disease, found largely in different countries.⁷⁸ Left untreated, both forms are invariably fatal. As of the 22nd WHO MEML, melarsoprol remains the only drug available to treat the 2nd stage of the fast-onset acute form of the disease caused by *Trypanosoma brucei rhodesiense* (other drugs are available for earlier stages, and for the form caused by *Trypanosoma brucei gambiense*).

The natural element arsenic, meanwhile, is most notorious as a poison, widely employed by the Borgias of Italy and the antagonists of countless mystery novels.⁷⁹ Nevertheless, it has also long been employed for medical purposes.⁸⁰ The basic idea of treating sleeping sickness with arsenic has a lengthy pedigree, going back at least as far as the famed explorer David Livingstone.⁸¹ In turn, it was a Canadian doctor, Harold Wolferstan Thomas, who published early experiments on the effectiveness of an arsenic compound, arsanic acid (given the overly optimistic name Atoxyl) in 1905.⁸² Experiments continued to find less noxious variations, culminating in the 1940s with the combination of an arsenic compound with dimercaprol, a drug used to treat poisoning by arsenic and other heavy metals.⁸³ Dimercaprol (also known as British anti-Lewisite) is found on the WHO MEML in

reflects some of the subtleties lost by a shift towards the terminology of Neglected Tropical Diseases (NTDs).

⁷⁸ At the time of submission, *Trypanosoma brucei gambiense* was found in 24 West and Central African countries, and *Trypanosoma brucei rhodesiense* in 13 East and Southern African countries, with only Uganda historically host to both. Happily, this number is decreasing. World Health Organization, “Trypanosomiasis, human African (sleeping sickness)” (10 January 2022), online: <[https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-\(sleeping-sickness\)](https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness))>.

⁷⁹ According to one analysis, it was also the poison most commonly used in homicides in Europe and the United States during the 19th Century. See Blum, Deborah, *The poisoner's handbook: murder and the birth of forensic medicine in Jazz Age New York* (2014) at p.79.

⁸⁰ Gibaud, Stéphane & Gérard Jaouen, “Arsenic-Based Drugs: From Fowler’s Solution to Modern Anticancer Chemotherapy” in Gérard Jaouen & Nils Metzler-Nolte, eds, *Medicinal Organometallic Chemistry* Topics in Organometallic Chemistry (Berlin, Heidelberg: Springer Berlin Heidelberg, 2010) 1.

⁸¹ Contrary to what one might presume of Dr. Livingstone, his attempts involved treatment of a horse, not a human. Livingstone, D, “Arsenic as a Remedy for the Tsetse Bite” (1858) s4-1:70 BMJ 360–361, online: <<https://www.bmj.com/lookup/doi/10.1136/bmj.s4-1.70.360-a>>.

⁸² See e.g., Thomas, H W. “Some Experiments in the Treatment of Trypanosomiasis” (1905) 1:2317 British Medical Journal 1140–1143.

⁸³ Friedheim, E A H. “Mel B in the treatment of human trypanosomiasis” (1949) 29:2 The American Journal of Tropical Medicine and Hygiene 173–180.

its own right; once poison and antidote were put together, the result was melarsoprol, hailed as a less toxic alternative at the time of its creation.⁸⁴

That melarsoprol remains the only option for 2nd stage *Tb rhodesiense* is highly unfortunate, because it is a remarkably unpleasant drug; colloquially, it has been referred to as a cocktail of arsenic and antifreeze.⁸⁵ As this evocative description suggests, it has very severe side effects. The most horrifying of these is that melarsoprol itself kills between 3-10% of those who take it.⁸⁶ In those that survive, it can cause intense burning sensations. And in case these awful side effects weren't enough, there is concern that the parasite is becoming increasingly resistant to melarsoprol.⁸⁷ All of this should be – and indeed has long been – ample demonstration of the need for better treatments for sleeping sickness. As Butler writes of melarsoprol, “Imagine the outcry in North America or Europe if a drug for, say, congestive heart disease didn't work in one-third of patients, and killed up to 10% of those who took it”.⁸⁸ It does seem exceedingly unlikely that melarsoprol would remain unbettered as the standard of care for over 70 years if it were a drug for a disease that primarily affected well-heeled denizens of high-income countries. In the absence of superior treatments, however, and given that the outcome of untreated 2nd stage *Tb rhodesiense* sleeping sickness is invariably death, melarsoprol remains an Essential Medicine.

This dearth of safe, effective tools is not restricted to endemic countries. Melarsoprol's utility is recognized by the Public Health Agency of Canada.⁸⁹ It has even been identified in the Canadian context, at least as recently as the 1980s, as

⁸⁴ Steverding, Dietmar. “The development of drugs for treatment of sleeping sickness: a historical review” (2010) 3:1 Parasites Vectors 15, online: <<http://parasitesandvectors.biomedcentral.com/articles/10.1186/1756-3305-3-15>>.

⁸⁵ See e.g., Ebikeme, Charles, “The death and life of the resurrection drug” (2014) 8:7 PLoS Negl Trop Dis e2910.

⁸⁶ Death is a result of a side-effect known as post-treatment reactive encephalopathy (PTRE). MacGregor, Paula & Keith R Matthews, “New discoveries in the transmission biology of sleeping sickness parasites: applying the basics” (2010) 88:9 J Mol Med (Berl) 865–871.

⁸⁷ Fairlamb, Alan H & David Horn. “Melarsoprol Resistance in African Trypanosomiasis” (2018) 34:6 Trends in Parasitology 481–492.

⁸⁸ Butler, Declan. “Tropical diseases: raiding the medicine cabinet” (2003) 424:6944 Nature 10–11.

⁸⁹ Public Health Agency of Canada, “Pathogen Safety Data Sheets: Infectious Substances – Trypanosoma brucei ssp.”, (22 October 2014), online: <<https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/trypanosoma-brucei-pathogen-safety-data-sheet.html>>.

being *safer and more effective* than the alternatives.⁹⁰ Indeed, the importance of ensuring access to existing medicines for sleeping sickness in non-endemic HICs like Canada has been repeatedly underscored for decades, along with accounts of the barriers to such access.⁹¹ In the 1970s, treatment for sleeping sickness was the specific example proffered to illustrate the need to establish tropical medicine depots for rarely used drugs in Canada (an idea revisited later).⁹² In the mid-1980s, melarsoprol was highlighted as a drug “particularly difficult to obtain” in Canada.⁹³ Such access barriers have come to the fore in other non-endemic HICs, as highlighted in the case of a multinational cluster of European tourists infected in the same national parks in Tanzania and diagnosed after returning to their respective countries.⁹⁴ At the same time, melarsoprol itself is not the oldest, or even the second oldest, drug for the treatment of African trypanosomiasis still found on the WHO MEML.⁹⁵ As such, melarsoprol and other longstanding Essential Medicines for sleeping sickness offer a valuable historical perspective on how and why research and treatment priorities can shift over time, from periods where numerous treatments were developed to decades of total neglect despite the obvious need for both innovation and continued access to treatment.

Given its status as a consummate Neglected Disease today, what drove the push to innovate treatments for African trypanosomiasis from the late 19th Century through the first half of the 20th Century? The answer remains one of money and

⁹⁰ White, G.F. & M.J. Davis, “Antiparasitic drugs: availability and regulatory requirements for ‘emergency’ supply” (1985) 132:3 Can Med Assoc J 273–274. Here it is compared to tryparsamide, another arsenic-based sleeping sickness drug, this one developed in the 1920s. See e.g., Pearce, L, “Tryparsamide treatment of African sleeping sickness” (1925) 61:1569 Science 90–92, online: <<https://www.sciencemag.org/lookup/doi/10.1126/science.61.1569.90-b>>.

⁹¹ See e.g., Moore, David AJ, “African Trypanosomiasis in Travelers Returning to the United Kingdom” (2002) 8:1 Emerg Infect Dis 74–76, online: <<http://www.cdc.gov/ncidod/eid/vol8no1/01-0130.htm>>; White, G.F. & M.J. Davis, “Antiparasitic drugs: availability and regulatory requirements for ‘emergency’ supply” (1985) 132:3.

⁹² Seah, S K, “Editorial: Canada and international health” (1976) 115:5 Can Med Assoc J 377–378.

⁹³ White, G.F. & M.J. Davis, “Antiparasitic drugs: availability and regulatory requirements for ‘emergency’ supply” (1985) 132:3 Can Med Assoc J 273–274.

⁹⁴ Jelinek, Tomas et al., “Cluster of African trypanosomiasis in travelers to Tanzanian national parks” (2002) 8:6 Emerg Infect Dis 634–635.

⁹⁵ Pentamidine dates from the 1930s, suramin from the 1920s. Steverding, Dietmar. “The development of drugs for treatment of sleeping sickness: a historical review” (2010) 3:1 Parasites Vectors 15, online: <<http://parasitesandvectors.biomedcentral.com/articles/10.1186/1756-3305-3-15>>.

markets, though in a different form than in the current day. At the time, the vast majority of Africa was still under the control of foreign powers; sleeping sickness was a major barrier to the colonization and commercialization of the continent. This ensured that finding a cure was a priority for colonial powers and their medical experts. Indeed, there is some grim irony to the fact that many of the first medicines for Neglected Diseases were originally developed as tools necessary for the conquest and exploitation of tropical territories by colonial powers located in more temperate climes. Overcoming sleeping sickness, as well as more widespread diseases like yellow fever and malaria, was key to colonial ambitions. The use of medicine as an explicit tool of colonization was itself normalized within the medical profession; as but one example, consider the President's Address at the American Medical Association's 60th Annual Session in 1909, highlighting the importance of such medical advances in a lecture entitled "The Conquest of the Tropics for the White Race".⁹⁶ Even today, resources and research in Neglected Diseases are still disproportionately concentrated in countries outside the tropics, a legacy of schools of tropical medicine established in major cities of colonial powers, like Amsterdam, Antwerp, Liverpool, London and Marseille. Some medicines employed to such ends remain inseparable from the colonial experience; indeed, the gin and tonic – the quintessential beverage to be sipped on a veranda by a pith-helmeted sahib as the sun sets over the empire – was developed by the British in India as a more palatable means of consuming the anti-malarial drug quinine.⁹⁷ Quinine, in use for two centuries, also remains a modern-day Essential Medicine.⁹⁸

⁹⁶ Gorgas, W C. "The Conquest of the Tropics for the White Race: President's Address at the Sixtieth Annual Session of the American Medical Association, at Atlantic City, June 9, 1909" (1909) LII:25 JAMA 1967, online:

<<http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.1909.25420510001001>>.

⁹⁷ Though there is perhaps some question of how effective the G&T approach really was; see e.g., Meyer, Christian G, Florian Marks & Jurgen May, "Editorial: Gin tonic revisited" (2004) 9:12 Trop Med Int Health 1239–1240, online: <<http://doi.wiley.com/10.1111/j.1365-3156.2004.01357.x>>.

⁹⁸ Though it too has its drawbacks. It will also be revisited in the Canadian context. See e.g., Achan, Jane et al., "Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria" (2011) 10 Malar J 144.

Just as they scrambled for territory, rivalries emerged between countries in tackling the diseases they encountered.⁹⁹ Such efforts also provided an additional excuse for colonialism in the guise of ostensibly benevolent humanitarianism, with colonizing powers justifying their control through aiding the locals in times of pestilence.¹⁰⁰ Against this backdrop, sleeping sickness offers perhaps the most extreme example of the intersection of colonialism and advances in tropical medicine. A zoonotic disease, sleeping sickness threatens not only manpower but livestock; in turn, shifts in trade and migratory patterns as an immediate consequence of colonialism also led directly to new epidemics.¹⁰¹ In response, as Headrick describes, the different major colonial powers in Africa – Britain, France, Belgium, Germany and Portugal – all took different approaches to tackling the disease.¹⁰² In contrast to pharmaceutical industry disinterest today, tackling the problem also attracted high-profile attention from some of the most famous scientific minds – and national public health heroes – of the era. For instance, the renowned German physician Robert Koch – whose Nobel Prize-winning work on tuberculosis blazed a trail for other subject matter covered in this thesis – investigated sleeping sickness in what was then German East Africa.¹⁰³ Demonstrating that even legendary experts don't always get it right, his findings would lead to one of the weirder treaty clauses in the annals of international health law, in which the UK and Germany agreed to exterminate crocodiles in their East

⁹⁹ See e.g., Bynum, W.F., "Policing hearts of darkness: aspects of the international sanitary conferences" (1993) 15:3 *Hist Philos Life Sci* 421–434. However, such national rivalries were not necessarily absolute; see e.g., Neill, Deborah, "Paul Ehrlich's Colonial Connections: Scientific Networks and Sleeping Sickness Drug Therapy Research, 1900-1914" (2008) 22:1 *Social History of Medicine* 61–77, online: <<https://academic.oup.com/shm/article-lookup/doi/10.1093/shm/hkn094>>.

¹⁰⁰ Tilley, Helen, "Medicine, Empires, and Ethics in Colonial Africa" (2016) 18:7 *AMA Journal of Ethics* 743–753, online: <<https://journalofethics.ama-assn.org/article/medicine-empires-and-ethics-colonial-africa/2016-07>>.

¹⁰¹ Headrick, Daniel R, "Sleeping sickness epidemics and colonial responses in East and Central Africa, 1900-1940" (2014) 8:4 *PLoS Negl Trop Dis* e2772.

¹⁰² Headrick, Daniel R, "Sleeping sickness epidemics and colonial responses in East and Central Africa, 1900-1940" (2014) 8:4 *PLoS Negl Trop Dis* e2772.

¹⁰³ Correa, Silvio Marcus de Souza, "Combating' tropical diseases in the German colonial press" (2013) 20:1 *Hist cienc saude-Manguinhos* 69–91, online: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0104-59702013000100005&lng=pt&tlng=pt>.

African territories as a means of controlling the disease.¹⁰⁴ By this time, purported breakthroughs like arsanilic acid were being heralded in the scientific literature not only as being capable of saving “millions of human lives”, but of making “vast tracts of country, now uninhabitable by civilized man on account of the ravages of animal pests, inhabitable and capable of cultivation”.¹⁰⁵

The search for effective sleeping sickness drugs took an even more overtly geopolitical turn in the early 1920s, when the German pharmaceutical firm Bayer allegedly attempted to trade their new sleeping sickness treatment “Bayer 205” in exchange for the return of Germany’s colonial empire lost during the First World War.¹⁰⁶ That barter proved unsuccessful, but the drug, now known as suramin, is still on the WHO MEML for first stage *Tb rhodesiense* infection.¹⁰⁷ Unusually, however, for a drug mentioned in this thesis, it is also still produced by Bayer, who sells it in certain markets – Canada not among them – under the historically evocative tradename Germanin. Another Essential Medicine, pentamidine, would follow in the 1930s, before melarsoprol arrived in the late 1940s.¹⁰⁸

The Essential Medicines melarsoprol, suramin, and pentamidine are all thus colonial relics of the first half of the 20th Century. Only pentamidine would ever become widely available in high-income countries, and only half a century later, after it was found to be effective in treating *Pneumocystis jirovecii* pneumonia, an

¹⁰⁴ Koch, Robert, “Über den bisherigen Verlauf der deutschen Expedition zur Erforschung der Schlafkrankheit in Ostafrika” (1906), online: <<https://edoc.rki.de/handle/176904/5215>>. He identified the crocodile as a possible host for the parasite. Highlighting how evidence-informed legal measures depend upon the quality of the evidence, this observation undergirded the bizarre provision obligating both states to “Take all such steps as are practicable for the destruction within their respective territories of crocodiles and other migratory animals which may be reasonably suspected of being a source of aliment to the *glossina palpalis* [the tsetse fly]”. *Agreement and protocol between the United Kingdom and Germany with regard to Sleeping Sickness* (1908), Art.5, online: <<https://wellcomecollection.org/works/rfvxsrt7>>.

¹⁰⁵ Boyce, Rubert, “The Treatment of Sleeping Sickness and Other Trypanosomiasis by the Atoxyl and Mercury Method” (1907) 2:2437 *Br Med J* 624–625.

¹⁰⁶ Pope, W J. “Synthetic Therapeutic Agents” (1924) 1:3297 *British Medical Journal* 413–414; “To Exchange: A Chemical for a Colony” (1923) 16:1 *The Scientific Monthly* 105–107. It is not entirely clear from these sources how serious this demand was, or indeed who issued the demand.

¹⁰⁷ Its discovery even drew editorial comment in the *Canadian Medical Association Journal*. “A New Remedy, Bayer 205” (1924) 14:3 *Can Med Assoc J* 249.

¹⁰⁸ Sands, Michael, Michael A Kron & Richard B Brown, “Pentamidine: a review” (1985) 7:5 *Rev Infect Dis* 625–634; Steverding, Dietmar. “The development of drugs for treatment of sleeping sickness: a historical review” (2010) 3:1 *Parasites Vectors* 15, online: <<http://parasitesandvectors.biomedcentral.com/articles/10.1186/1756-3305-3-15>>.

important infection of persons with HIV.¹⁰⁹ In the meantime, without the engine of colonial commerce behind it, development of novel treatments for the diseases of now independent former colonies has not kept up its former pace.¹¹⁰ Furthermore, coinciding with the tail end of the colonial era, reforms to pharmaceutical regulation in the wake of the thalidomide tragedy of the early 1960s also increased the obligations required of pharmaceutical companies in order to bring medicines to market, with the side-effect of further decreasing interest in pursuing drugs in less profitable fields like tropical medicine.¹¹¹ In 2007, the WHO Expert Committee on the Use of Essential Drugs reviewed the sleeping sickness drugs on the WHO MEML. Their often-serious side effects were acknowledged.¹¹² Ultimately, however, recognizing “the public health importance of supporting access to the few treatments available for sleeping sickness”, the Committee recommended they should all remain included on the core list of the MEML.¹¹³ In other words, they are not ideal drugs, but there are no better alternatives available for treating a serious disease. The fact that multiple drugs for sleeping sickness which emerged during the colonial era are still on the WHO MEML is a reminder of how the disease they treat has been neglected once tackling it no longer promised to assist in the hegemonic goals of powerful states.

The first Essential Medicine for sleeping sickness of the post-colonial era illustrates another important aspect of Essential Medicines relevant to the topic at hand: the same medicine may have very different uses, and those uses may be

¹⁰⁹ Note: *P. jirovecii* was previously known as *P. carinii*. Sands, Michael, Michael A Kron & Richard B Brown, “Pentamidine: a review” (1985) 7:5 Rev Infect Dis 625–634. It would also become an early example of an old drug being exploitatively priced upon formal approval. See e.g., Steinbrook, Robert, “Firm’s Sharp Price Increase for AIDS Drug Attacked”, *Los Angeles Times* (31 October 1987), online: <<https://www.latimes.com/archives/la-xpm-1987-10-31-mn-4490-story.html>>.

¹¹⁰ Pécoul, Bernard, “New drugs for neglected diseases: from pipeline to patients” (2004) 1:1 PLoS Med e6.

¹¹¹ This topic will be explored in greater depth later, but see e.g., Mikami, Koichi, “Orphans in the Market: The History of Orphan Drug Policy” (2019) 32:3 Social History of Medicine 609–630, online: <<https://academic.oup.com/shm/article/32/3/609/4663001>>.

¹¹² WHO Expert Committee on the Use of Essential Drugs, ed, *The selection and use of essential medicines: report of the WHO Expert Committee, 2005 (including the 14th model list of essential medicines)* WHO technical report series 933 (Geneva, 2006) at p.41.

¹¹³ WHO Expert Committee on the Use of Essential Drugs, ed, *The selection and use of essential medicines: report of the WHO Expert Committee, 2005 (including the 14th model list of essential medicines)* WHO technical report series 933 (Geneva, 2006) at p.42.

prioritized very differently in different settings. To wit, a 2001 commentary in the *Journal of the American Academy of Dermatology* begins:

To many dermatologists in the United States, the recent approval by the Food and Drug Administration (FDA) of topical eflornithine as a treatment for facial hirsutism in women represents the debut of a completely new human drug. For some, the mention of African sleeping sickness may activate long-dormant memories of microbiology courses that have been, at best, peripherally relevant to their subsequent careers in dermatology.¹¹⁴

Such is the lot of eflornithine in high-income settings. Originally developed (unsuccessfully) as a cancer drug in the 1970s, it was found to be effective against *Tb gambiense*. To encourage drug development in this now overlooked area, sleeping sickness itself had been designated a “rare disease” in the context of Orphan Drug legislation in the United States, underscoring parallels between Neglected Diseases and Rare Diseases that will be revisited later on.¹¹⁵ Eflornithine ultimately received Orphan Drug status for sleeping sickness, and the US FDA approved it for this use in 1990, under the tradename Ornidyl.¹¹⁶ Then, in a pattern that will become quite familiar over the course of this thesis, a series of mergers and acquisitions occurred, taking the drug from Merrell Dow, to Marion Merrell Dow, to Hoechst Marion Roussel, to Aventis (and now Sanofi). By 1995, despite reaping the advantages of Orphan Drug status in the United States, and the ongoing public health need in Africa, Aventis indicated that as a cost-reduction measure it

¹¹⁴ Coyne, Philip E, “The eflornithine story” (2001) 45:5 *Journal of the American Academy of Dermatology* 784–786, online:

<<https://linkinghub.elsevier.com/retrieve/pii/S0190962201858801>>.

¹¹⁵ National Institutes of Health, List of Orphan FDA Orphan Drugs, online:

<<https://rarediseases.info.nih.gov/diseases/fda-orphan-drugs/>>.

¹¹⁶ Coyne, Philip E, “The eflornithine story” (2001) 45:5 *Journal of the American Academy of Dermatology* 784–786, online:

<<https://linkinghub.elsevier.com/retrieve/pii/S0190962201858801>>; see also Ebikeme, Charles, “The death and life of the resurrection drug” (2014) 8:7 *PLoS Negl Trop Dis* e2910.

would stop producing Ornidyl. Aventis donated remaining its stocks, due to expire in 1999, to the humanitarian organization Médecins Sans Frontières (MSF).¹¹⁷

This might have marked the end of eflornithine, if not for another pharmaceutical company, Bristol Myers Squibb, who, under licence from Aventis, was moving forward with another more lucrative use: the topical hair removal cream Vaniqa, which received US FDA approval in 2000 (and from Health Canada in 2005).¹¹⁸ The extreme juxtaposition of these two products, and the evident willingness of the pharmaceutical industry to sell cosmetic cream to women in wealthy countries while abandoning people in Africa to an inevitably fatal disease helped create sufficient pressure to push the pharmaceutical companies to reach an agreement with the WHO to resume limited production of eflornithine and donate it to WHO programs.¹¹⁹ Similar pressure also yielded commitments for further drugs from other companies, such as Bayer, who had similarly threatened to cease production of its own Essential Medicines for sleeping sickness.¹²⁰ Thus, a commercial beauty product in HICs helped draw attention to the neglect of Neglected Diseases and resume access, albeit precariously and at the whim of pharmaceutical companies, to a discontinued Essential Medicine. Commercially, Ornidyl has been permanently discontinued in the United States; it was never marketed in Canada. Vaniqa remains on the market (though it has changed hands in the interim; Canadian rights are now held by Cipher Pharmaceuticals Inc.); it is the only eflornithine product formally available in either country.

¹¹⁷ Ebikeme, Charles, "The death and life of the resurrection drug" (2014) 8:7 PLoS Negl Trop Dis e2910.

¹¹⁸ Coyne, Philip E, "The eflornithine story" (2001) 45:5 Journal of the American Academy of Dermatology 784–786, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0190962201858801>>; see also Ebikeme, Charles, "The death and life of the resurrection drug" (2014) 8:7 PLoS Negl Trop Dis e2910.

¹¹⁹ Boseley, Sarah, "Drug firm wakes up to sleeping sickness", *The Guardian* (7 May 2001), online: <<https://www.theguardian.com/world/2001/may/07/medicalscience.businessofresearch>>; McNeil Jr, Donald G, "Cosmetic Saves a Cure for Sleeping Sickness", *The New York Times* (9 February 2001), online: <<https://www.nytimes.com/2001/02/09/world/cosmetic-saves-a-cure-for-sleeping-sickness.html>>.

¹²⁰ Bayer's drugs were suramin and nifurtimox, the latter of which emerged at the tail end of the colonial period and will be revisited in the context of Chagas disease. See e.g., Etchegorry, M Gastellu et al., "Availability and affordability of treatment for Human African Trypanosomiasis" (2001) 6:11 Trop Med Int Health 957–959, online: <<http://doi.wiley.com/10.1046/j.1365-3156.2001.00764.x>>.

Fortunately, this section need not end entirely on a depressing note; the addition of fexinidazole, the first all-oral treatment for sleeping sickness, to the WHO MEML in 2019 is a positive reminder that important innovations are still possible in treating Neglected Diseases, even if they do not happen as often as they should.¹²¹ Its development was driven not by commercial pharmaceutical companies, but by the non-profit Drugs for Neglected Diseases Initiative (DNDi).¹²² Unfortunately, however, its inclusion on the WHO MEML is thus far only for treatment of *Tb gambiense*; there still remains no alternative to melarsoprol. As such, the fact that some of the far from perfect drugs found on the WHO MEML remain Essential Medicines is a potent demonstration that drug development has long been driven by commercial considerations rather than public health need. In turn, that many of these existing drugs have teetered on the brink of vanishing from global production entirely is a stark reminder of the continued risks of a system reliant on commercial interest for access to Essential Medicines. The fact that, of the six Essential Medicines for sleeping sickness, only one is available in an appropriate form in Canada (and must be used off-label) also makes it lucky that cases in Canada have been very rare.¹²³

Before closing this section, it is also worth highlighting one small example of how these worlds meet in a Canadian regulatory context, as a taste of things to come. In the late 1980s, after a multi-year process, Health Canada banned arsenic

¹²¹ It should be noted that adding a drug like fexinidazole, only recently approved anywhere in the world rather than boasting a lengthy history of use, to the WHO MEML is a scenario that raises its own set of issues and has been a source of controversy. At the same time, this underscores the urgent need for such innovation for diseases like sleeping sickness. The questions raised by this scenario will have to wait for a future thesis focused on novel, rather than decades-old, Essential Medicines.

¹²² Deeks, Emma D, "Fexinidazole: First Global Approval" (2019) 79:2 *Drugs* 215–220.

¹²³ As noted earlier, the exception is pentamidine, indicated on the WHO MEML for 1st stage *T. brucei gambiense*; however, in Canada, it is only indicated for *Pneumocystis jirovecii*, meaning its use for sleeping sickness is off label. Vaniqa's topical formulation of eflornithine is not useful for sleeping sickness. Sleeping sickness is not a reportable disease in Canada, so it is not clear that published reports capture every case, though it is unlikely there are a large number missing. See e.g., Davis, J et al., "Fever, headache, fatigue and chancre in a traveller returning from Tanzania" (2012) 23:3 *Can J Infect Dis Med Microbiol* 108–109; Mighelsen, Stephanie J et al., "Human African trypanosomiasis: a review of non-endemic cases in the past 20 years" (2011) 15:8 *International Journal of Infectious Diseases* e517–e524; Seah, S K & K M Flegel, "African trypanosomiasis in Canada" (1972) 106:8 *Can Med Assoc J* 902–903; Simarro, Pere P et al., "Human African Trypanosomiasis in Non-Endemic Countries (2000–2010)" (2012) *J Travel Med* 19:1 44–53.

as an ingredient in any drug for human use.¹²⁴ As emerged in consultations after the initial proposal was published, this change posed a threat to access to existing medicines like melarsoprol for Neglected Diseases like African trypanosomiasis. That banning an ingredient on safety grounds would impact access to an Essential Medicine for a Neglected Disease simultaneously highlights both the deficiencies of such drugs and the lack of alternatives. The result was a clarification in the *Canada Gazette*: “Arsenical products used to treat tropical diseases will continue to be available through the Emergency Drug Release Program”.¹²⁵ Thus, not for the first or last time, Canadian standards for the safety and quality of pharmaceutical products had to be worked around – in this instance explicitly – in order to maintain access to Essential Medicines for Neglected Diseases that are not available in Canada even as they remain necessary for the treatment of Canadian patients.

¹²⁴ C.01.040(b), *Food and Drug Regulations* (SOR/89-229, s. 4) (C.R.C., c. 870). It should be noted the ban on arsenic was subsequently modified in 2013 (SOR/2013-113, s. 1) to permit the sale of arsenic trioxide, which has since been added to the WHO MEML, not as a treatment for Neglected Diseases but for leukemia.

¹²⁵ The Emergency Drug Release Program (EDRP) was the antecedent of the SAP; both will be discussed at length later. *Canada Gazette Part II*, Vol. 123, No.10, 5 October 1989 at p.3.

Chapter 1: Access to Off-Patent Essential Medicines for Neglected Diseases in Canada

Nobel Prize-worthy, but not market-worthy

The 2015 Nobel Prize in Physiology or Medicine was split between the discoverers of two cornerstones of global health programmes. The Nobel Institute described these discoveries as follows:

William C. Campbell and Satoshi Ōmura discovered a new drug, Ivermectin, the derivatives of which have radically lowered the incidence of River Blindness and Lymphatic Filariasis, as well as showing efficacy against an expanding number of other parasitic diseases. Youyou Tu discovered Artemisinin, a drug that has significantly reduced the mortality rates for patients suffering from Malaria. These two discoveries have provided humankind with powerful new means to combat these debilitating diseases that affect hundreds of millions of people annually. The consequences in terms of improved human health and reduced suffering are immeasurable.¹²⁶

The landmark papers describing these discoveries cited by the Nobel Committee were published in 1979 and 1981, respectively.¹²⁷ Since then, both ivermectin (the key drug derived from avermectin), and malaria therapies containing artemisinin derivatives like artemether and artesunate have become vital tools for public health, including in many of the poorest communities on Earth. Both discoveries emerged a few years after the Essential Medicines concept had been formalized by the World Health Organization and the inaugural WHO MEML released; by the time

¹²⁶ The Nobel Assembly at Karolinska Institutet. *Press Release - 2015 Nobel Prize in Physiology or Medicine* (Nobel Foundation, 2015), online: <<https://www.nobelprize.org/uploads/2018/06/press-29.pdf>>.

¹²⁷ Burg, R W et al. "Avermectins, New Family of Potent Anthelmintic Agents: Producing Organism and Fermentation" (1979) 15:3 *Antimicrobial Agents and Chemotherapy* 361–367, online: <<http://aac.asm.org/cgi/doi/10.1128/AAC.15.3.361>>; Egerton, J R et al. "Avermectins, New Family of Potent Anthelmintic Agents: Efficacy of the B1a Component" (1979) 15:3 *Antimicrobial Agents and Chemotherapy* 372–378, online: <<http://aac.asm.org/cgi/doi/10.1128/AAC.15.3.372>>; Tu, Y Y et al. "[Studies on the constituents of *Artemisia annua* L.]" (1981) 16:5 *Yao Xue Xue Bao* 366–370.

the Nobel Prize was handed out, however, these drugs were off-patent, and firmly entrenched on the WHO MEML.¹²⁸

At the time the Nobel Prize was awarded, neither Essential Medicine was commercially available for human use in Canada. Furthermore, no version of either drug had ever been marketed for human use in this country. The fact that neither of the drugs worthy of such a prestigious honour had ever been formally available to Canadian patients after decades of widespread use elsewhere is a stark illustration of how medical value does not inevitably lead to market approval.¹²⁹ This is not to say that a Nobel Prize should dictate in perpetuity what treatments should be available, but it does suggest a rebuttable presumption.¹³⁰ In 2015 there was no novel evidence, nor a superior alternative, that might underpin such a rebuttal for either drug. This remains true in 2022. Each of these drugs serves to illustrate some of the barriers faced when trying to access off-patent Essential Medicines for Neglected Diseases in Canada.

Artemisinin

The fact that a disease does not rank among those exerting the greatest public health burden in Canada, or even that it is not – currently – endemic to Canada, does not mean Canadians are not affected, or that they do not require treatment. It is true that the Great White North, while no stranger to mosquitoes, is one of the countries least likely to be associated with malaria in the popular imagination.

¹²⁸ Ivermectin was first added in 1987; artemether was added in 1997 and artesunate in 1999. All have been added for further indications or as part of additional combination drugs since.

¹²⁹ Picard, André, “Nobel-worthy drugs, virtually unseen in Canada”, *Globe and Mail* (13 October 2015), online: <<https://www.theglobeandmail.com/opinion/nobel-worthy-drugs-virtually-unseen-in-canada/article26760859/>>.

¹³⁰ As one such rebuttal, overlapping with the subject matter of this thesis on multiple levels, one need only think of Julius Wagner-Jauregg, who was awarded the Nobel Prize in Physiology or Medicine in 1927 for his “discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica”.¹³⁰ *The Nobel Prize in Physiology or Medicine 1927* (NobelPrize.org), online: <<https://www.nobelprize.org/prizes/medicine/1927/summary/>>. In plainer language, by intentionally infecting patients with malaria, he could induce a fever that would kill the spirochetes that caused syphilis. This treatment was adopted in Canada and used for some time afterwards, see e.g., Crawford, CM, “Treatment of Paretic Neurosyphilis by Malaria and Tryparsamide” (1940) 31:3 *Canadian Public Health Journal* 99–105. This approach, while the most effective available at the time, has been superseded. This is exactly how it should be, however, including when it comes to Essential Medicines, whatever their initial pedigree: Safer and more effective treatments should supersede less effective or more dangerous ones.

Nonetheless, as in the United States and much of Europe, malaria was once found in Canada.¹³¹ Lawmakers on Parliament Hill, spurred to action by reading this thesis, could look out their windows at the Rideau Canal for further inspiration, as its construction continued the long global tradition of canal workers being at serious peril from the disease, with reports of a peak infection rate of near 60% and a mortality of 4%.¹³²

Today, malaria is no longer endemic in Canada. Nonetheless, in the 21st Century, Canada has had close to 500 cases almost every year.¹³³ This includes migrants from endemic countries, as well as people travelling for both business and pleasure.¹³⁴ Even in the 21st Century, some of these cases result in serious illness and even death.¹³⁵ This is a problem today; as for tomorrow, there is a risk that malaria, like other diseases more closely associated with warmer climates, could re-establish itself in Canada as the result of climate change, whether through existing vectors or newly established ones.¹³⁶ Indeed, where the parasite has been

¹³¹ See e.g., Fallis, A Murray. "Malaria in the 18th and 19th centuries in Ontario." (1984) 1:2 Canadian Bulletin of Medical History 25–38, online: <<https://utpjournals.press/doi/10.3138/cbmh.1.2.25>>; Fisk, G H. "Malaria and the Anopheles Mosquito in Canada" (1931) 25:6 Canadian Medical Association Journal 679–683; MacLean, J D & B J Ward, "The return of swamp fever: malaria in Canadians" (1999) 160:2 CMAJ 211–212.

¹³² Wylie, William N T. "Poverty, Distress, and Disease: Labour and the Construction of the Rideau Canal, 1826–32" (1983) 11 Labour / Le Travail 7, online: <<https://www.jstor.org/stable/10.2307/25140199?origin=crossref>>.

¹³³ Boggild, Andrea K et al. "Underestimate of annual malaria imports to Canada" (2017) 17:2 The Lancet Infectious Diseases 141–142, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1473309917300105>>; MacLean, J Dick et al. "Malaria Epidemics and Surveillance Systems in Canada" (2004) 10:7 Emerg Infect Dis 1195–1201, online: <http://wwwnc.cdc.gov/eid/article/10/7/03-0826_article.htm>; Government of Canada. *Surveillance of malaria* (Government of Canada, 2016), online: <<https://www.canada.ca/en/public-health/services/diseases/malaria/surveillance-malaria.html>>.

¹³⁴ Boggild, Andrea K et al., "Malaria in travellers returning or migrating to Canada: surveillance report from CanTravNet surveillance data, 2004–2014" (2016) 4:3 CMAJ Open E352–E358, online: <<http://cmajopen.ca/lookup/doi/10.9778/cmajo.20150115>>.

¹³⁵ MacLean, J Dick et al., "Malaria epidemics and surveillance systems in Canada" (2004) 10:7 Emerg Infect Dis 1195–1201; McCarthy, Anne E et al., "Severe malaria in Canada, 2001–2013" (2015) 14:1 Malar J 151, online: <<https://malariajournal.biomedcentral.com/articles/10.1186/s12936-015-0638-y>>.

¹³⁶ Berrang-Ford, L et al. "Climate Change and Malaria in Canada: A Systems Approach" (2009) 2009 Interdisciplinary Perspectives on Infectious Diseases 1–13, online: <<http://www.hindawi.com/journals/ipid/2009/385487/>>; Ng, V et al. "Could exotic mosquito-borne diseases emerge in Canada with climate change?" (2019) 45:4 CCDR 98–107, online: <<https://www.canada.ca/content/dam/phac-aspc/documents/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2019-45/issue-4-april-4-2019/ccdrv45i04a04-eng.pdf>>.

introduced from abroad in recent decades, there have been credible reports of onward local transmission.¹³⁷ As such, malaria provides an effective illustration of numerous emerging public health concerns, from shifts in patterns of travel and migration as a result of globalization, to the potential impact of climate change on Canada's ecosystem, including the diseases (and their vectors) that are part of this ecosystem. The emergence of West Nile Virus, a mosquito-borne Neglected Disease first detected in Canada a mere twenty years ago that has since become endemic, should serve as further warning.¹³⁸ Nonetheless, malaria's impact on Canadians attracts relatively little attention, even though there have been more cases of malaria reported than of West Nile virus in all but three years since the latter first appeared in Canada.¹³⁹

Like malaria itself, artemisinin has a fascinating history.¹⁴⁰ In Chinese, it is known as qinghaosu, with both name and substance derived from qinghao (the Chinese name for *Artemisia annua*), a plant in the pharmacopeia of traditional Chinese medicine.¹⁴¹ It also provides a further illustration of how increased state attention to a Neglected Disease can drive innovation. In this case, the driver was not colonialization or commerce, but warfare. During their conflict with the United States (the conflict known in most Western countries as the Vietnam War), Vietnam requested assistance from China regarding effective antimalarial drugs. As part of this undertaking, both synthetic drugs and drugs derived from traditional medicine

¹³⁷ Baqi, M et al. "Malaria: Probably locally acquired in Toronto, Ontario" (1998) 9:3 The Canadian Journal of Infectious Diseases 183–184.

¹³⁸ Nosal, Bob & Rosanan Pellizzari, "West Nile virus" (2003) 168:11 CMAJ 1443–1444. For more on this Neglected Disease establishing itself in North America, see Ronca, Shannon E, Jeanne C Ruff & Kristy O Murray, "A 20-year historical review of West Nile virus since its initial emergence in North America: Has West Nile virus become a neglected tropical disease?" (2021) 15:5 PLoS Negl Trop Dis e0009190. Given the theme of this thesis, it should be noted that the world is still waiting for its first effective treatment for West Nile virus.

¹³⁹ Though it must be recognized that in two of those years, 2003 and 2007, there were major outbreaks of West Nile virus in Canada. Public Health Agency of Canada, "Reported cases from 1924 to 2019 in Canada - Notifiable diseases on-line", online: <<https://diseases.canada.ca/notifiable/charts?c=pl>>.

¹⁴⁰ While today outdated, this author opines that the most enjoyably readable history of malaria remains Harrison, Gordon A, *Mosquitoes, malaria, and man: a history of the hostilities since 1880*, 1st ed (New York: Dutton, 1978).

¹⁴¹ Indeed, it is frequently referenced as an example of the utility of traditional remedies in modern medicine, though this is not a topic that will be explored in this thesis. Tu, Youyou. "The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine" (2011) 17:10 Nat Med 1217–1220.

were explored.¹⁴² As China opened up relations to the rest of the world in the 1980s, this initial research was subsequently built upon.¹⁴³ Today, as a component of combination therapy (most famously artemether/lumefantrine), artemisinin is the backbone of global antimalarial treatment, particularly for the most serious form, caused by *P. falciparum*.¹⁴⁴

It is not, however, a component of any drug approved in Canada. Canadians do have domestic access to other treatments and prophylactics for malaria, like mefloquine (which is on the WHO MEML) and atovaquone-proguanil (which is not).¹⁴⁵ However, the drug considered the standard of care in much of the world is unavailable in Canada for the simple reason that its makers have not brought it to market here.¹⁴⁶ This presents an odd situation for treatment guidelines. Although the malaria treatment guidelines published by the Public Health Agency of Canada include combination therapy with an artemisinin derivative, they also explicitly note such treatment is not yet available in Canada.¹⁴⁷ Indeed, the most recent

¹⁴² Speaking of the side effects of Essential Medicines, involvement in this research, taking place at the height of the Cultural Revolution, may have served to save scientists and others who might otherwise have been purged. See e.g., Weiyuan, Cui. "Ancient Chinese anti-fever cure becomes panacea for malaria" (2009) 87:10 Bull World Health Organ 743–744.

¹⁴³ Faurant, C. "From bark to weed: the history of artemisinin" (2011) 18:3 Parasite 215–218.

¹⁴⁴ Combination therapy, rather than monotherapy, is important for preventing the development of drug resistance, a consistent problem in malaria treatment. Drug resistance will be revisited later.

¹⁴⁵ Atovaquone-proguanil is widely known under the tradename Malarone. Interestingly, no drug containing atovaquone is found on the WHO MEML. Mefloquine remains on the WHO MEML, but has become controversial in many countries, including both Canada and the US, in light of high-profile safety concerns, particularly as a result of use by the military. This has led to lawsuits being filed by veterans, see e.g., Haines, Avery, "Canadian veterans suing government over anti-malarial drug's adverse effects", CTV News (30 April 2019), online: <<https://www.ctvnews.ca/w5/canadian-veterans-suing-government-over-anti-malarial-drug-s-adverse-effects-1.4402691>>. For an interesting overview of the mefloquine issue, see Croft, Ashley M, "A lesson learnt: the rise and fall of Lariam and Halfan" (2007) 100:4 J R Soc Med 170–174.

¹⁴⁶ It should be noted that manufacturer willingness is not totally a one-way street. Novartis allegedly did enter into discussions with Health Canada about bringing Coartem (their proprietary artemether/lumefantrine combination treatment) to market in Canada but could not ultimately reach an agreement that would have sufficiently lowered the costs of market entry for Novartis to follow through (Amir Attaran, personal communication). This issue will be revisited.

¹⁴⁷ Boggild, A et al. "Summary of recommendations for the diagnosis and treatment of malaria by the Committee to Advise on Tropical Medicine and Travel (CATMAT)" (2014) 40:7 CCDR 133–143, online: <<https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/publicat/ccdr-rmtc/14vol40/dr-rm40-07/assets/pdf/ccdrv40i07a02-eng.pdf>>; Committee to Advise on Tropical Medicine and Travel & Public Health Agency of Canada, "Chapter 7 - Treatment of malaria: Canadian recommendations for the prevention and treatment of malaria" in Canadian recommendations for the prevention and treatment of malaria – CATMAT (Updated 2019), online:

update specifically – and perhaps optimistically – outlines alternatives to be used until “these agents [containing artemisinin derivatives] are available in Canada”.¹⁴⁸ There is, unfortunately, no indication of when this might be, or what steps if any are currently being taken to make this happen. In a further irony, chloroquine, the longstanding Essential Medicine that artemisinin derivatives have been vital in replacing in much of the world following the widespread emergence of chloroquine resistance, was discontinued from the Canadian market in 2021, even as it continues to play a central role in Canadian treatment guidelines in situations where chloroquine resistance is not an issue.¹⁴⁹

At the same time, in relation to its international aid programming, Canada has also stated that “as part of Canada’s support, the most effective antimalarial treatment (artemisinin-based combination therapies, or ACTs)... are being made available to patients in their own communities, where the need is most urgent”.¹⁵⁰ This places Canadian patients in an interesting position. No matter where they were infected, there is a good chance that the most effective treatment was more readily available there than upon their arrival in Canada.¹⁵¹ In fact, Canada’s

<<https://www.canada.ca/en/public-health/services/catmat/canadian-recommendations-prevention-treatment-malaria/chapter-7-treatment.html>>.

¹⁴⁸ Committee to Advise on Tropical Medicine and Travel & Public Health Agency of Canada, “Chapter 7 - Treatment of malaria: Canadian recommendations for the prevention and treatment of malaria” in Canadian recommendations for the prevention and treatment of malaria – CATMAT (Updated 2019), online: <<https://www.canada.ca/en/public-health/services/catmat/canadian-recommendations-prevention-treatment-malaria/chapter-7-treatment.html>>.

¹⁴⁹ This market departure followed longstanding shortages. See e.g., Northern Health Physicians, “Discontinued drug: Chloroquine 250 mg tablets” (30 July 2021), online: <<https://physicians.northernhealth.ca/newsroom/discontinued-drug-chloroquine-250-mg-tablets>>. Like artemisinin, chloroquine was also originally developed for use in wartime, in this case WWII; ironically, although discovered by Germany before the war, its true utility was not recognized until samples of a derivative were examined by the Americans during the conflict. See e.g., Coatney, G R, “Pitfalls in a discovery: the chronicle of chloroquine” (1963) 12 Am J Trop Med Hyg 121–128. For an example of a disturbing lag in policy shifts in response to chloroquine resistance, and the importance of artemisinin in its stead, see Attaran, Amir et al., “WHO, the Global Fund, and medical malpractice in malaria treatment” (2004) 363:9404 The Lancet 237–240, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673603153305>>. Chloroquine will be revisited, along with the related drug hydroxychloroquine, later in this thesis.

¹⁵⁰ Government of Canada. “Malaria in developing countries”, (6 August 2017), online: <https://www.international.gc.ca/world-monde/issues_developpement-enjeux_developpement/global_health-sante_mondiale/malaria-paludisme.aspx?lang=eng>.

¹⁵¹ It should be noted –and indeed is noted in Canada’s malaria guidelines – that the quality of antimalarials obtained in some countries can be a real concern. Committee to Advise on Tropical Medicine and Travel & Public Health Agency of Canada, “Chapter 7 - Treatment of malaria: Canadian

current treatment guidelines explicitly recognize the phenomenon of use by patients in Canada of artemisinin combination drugs acquired elsewhere.¹⁵² Adding a layer of irony is the fact this superior access to treatment abroad may have involved the direct support of the Canadian government.

The absence of artemisinin-based therapies from the Canadian market has serious repercussions for those in Canada unfortunate enough to need them. For instance, the consequences of not having timely access to the Essential Medicine parenteral artesunate – another artemisinin derivative, crucial for treatment of severe *P. falciparum* malaria – are so serious that it led to the creation of a dedicated Canadian access pathway in the early 2000s, even as the drug itself remained (and remains) unmarketed in Canada. Multiple deaths from malaria had been reported in Canada in the years immediately prior to this pathway being established.¹⁵³ As a result, the Canadian Malaria Network (CMN) was established, in collaboration with PHAC and the SAP, to permit supplies of parenteral artesunate (as well as parenteral quinine, another Essential Medicine for malaria similarly unmarketed in Canada) to be kept on hand in a small number of designated facilities in advance of patient need.¹⁵⁴ This is vital, as time is of the essence when treatment with parenteral artesunate is required; as such, the mere existence of this mechanism is a rebuke of the delays in obtaining unmarketed medicines in a

recommendations for the prevention and treatment of malaria” in Canadian recommendations for the prevention and treatment of malaria – CATMAT (Updated 2019), online: <https://www.canada.ca/en/public-health/services/catmat/canadian-recommendations-prevention-treatment-malaria/chapter-7-treatment.html>. See also Karunamoorthi, Kaliyaperumal, “The counterfeit anti-malarial is a crime against humanity: a systematic review of the scientific evidence” (2014) 13 Malar J 209. However, this is also an area where support for initiatives such as WHO Prequalification – discussed later – can help mitigate the problem of access to high-quality supplies.

¹⁵² Committee to Advise on Tropical Medicine and Travel & Public Health Agency of Canada, “Chapter 7 - Treatment of malaria: Canadian recommendations for the prevention and treatment of malaria” in Canadian recommendations for the prevention and treatment of malaria – CATMAT (Updated 2019), online: <<https://www.canada.ca/en/public-health/services/catmat/canadian-recommendations-prevention-treatment-malaria/chapter-7-treatment.html>>.

¹⁵³ Humar, A et al., “Fatal falciparum malaria in Canadian travellers” (1997) 156:8 CMAJ 1165–1167; Kain, K C et al., “Malaria deaths in visitors to Canada and in Canadian travellers: a case series” (2001) 164:5 CMAJ 654–659.

¹⁵⁴ Public Health Agency of Canada, “Medical Access to Artesunate or Quinine for Malaria Treatment Streamlined in Canada through the Canadian Malaria Network (CMN)”, online: <<https://www.canada.ca/en/public-health/services/travel-health/medical-access-artesunate-quinine-malaria-treatment.html>>.

timely manner through existing channels like the SAP.¹⁵⁵ In the first twelve years of the CMN's existence, drugs were accessed through it 295 times.¹⁵⁶ Of course, creating an entire mechanism to support access to two unmarketed Essential Medicines in order to ensure access to life-or-death treatment would not be necessary if they were formally available in Canada.

Reliance on unapproved sources also places access at the risk of running into other barriers already illustrated with unmarketed Essential Medicines for Neglected Diseases. Traditionally, the CMN has obtained its artesunate from the U.S. Army's Walter Reed Institute of Research.¹⁵⁷ For years, as in Canada, artesunate was treated as an unapproved but medically vital medicine in the US, which is why it was available from Walter Reed.¹⁵⁸ However, parenteral artesunate was finally approved by the US FDA in 2020, and came to the US market in 2021.¹⁵⁹ Unfortunately, rather than continuing to be distributed for free by Walter Reed, or sold at the cost of a few dollars in other parts of the world, a course of artesunate in the United States now costs roughly \$30,000USD.¹⁶⁰ This puts Canadian access through the CMN at risk of a price increase similar to cycloserine, barring steps to find an alternate source. As of this writing, that alternative source appears to be

¹⁵⁵ These delays are discussed at length later.

¹⁵⁶ McCarthy, Anne E et al., "Severe malaria in Canada, 2001–2013" (2015) 14:1 Malar J 151, online: <<https://malariajournal.biomedcentral.com/articles/10.1186/s12936-015-0638-y>>.

¹⁵⁷ See e.g., University Health Network, "Canadian Malaria Network - Distribution of Artesunate and Quinine: Guidelines for Pharmacy Staff", (24 June 2009), online: *Department of Pharmacy Services - Drug Information Service* <<https://eportal.mountsinai.ca/Microbiology//protocols/pdf/MalariaTreatment%20Distribution%20Guide%20Pharmacists.pdf>>.

¹⁵⁸ The American mechanism for access to unapproved drugs for Neglected Diseases will be discussed in more depth later.

¹⁵⁹ Amivas (US) LLC, "Amivas (US), LLC Announces U.S. Launch of Artesunate for Injection for Initial Treatment of Severe Malaria", (30 March 2021), online: <<https://www.prnewswire.com/news-releases/amivas-us-llc-announces-us-launch-of-artesunate-for-injection-for-initial-treatment-of-severe-malaria-301258501.html>>.

¹⁶⁰ Frosch, Anne EP, Aileen Ahiskali & Chandy C John, "Unaffordable treatment for severe malaria highlights U.S. drug market pitfalls", *STAT News* (11 June 2021), online: <<https://www.statnews.com/2021/06/11/unaffordable-treatment-for-severe-malaria-highlights-u-s-drug-market-pitfalls/>>. By contrast, a decade before, artesunate was referred to as the "more expensive" treatment, at a cost of \$1.06USD per vial. Lubell, Yoel et al., "Cost-effectiveness of parenteral artesunate for treating children with severe malaria in sub-Saharan Africa" (2011) 89:7 Bull World Health Organ 504–512.

Guilin Pharmaceuticals in China.¹⁶¹ While unapproved in Canada or the US, this supply has received WHO Prequalification, an international standard for pharmaceutical quality intended to be equivalent to a Stringent Regulatory Authority (SRA) like Canada or the United States. While shifting to this more affordable option from a supplier meeting internationally recognized standards is a positive step – one that will be revisited in detail later – it is still a shift being made for a single Essential Medicine which remains absent from the Canadian market despite being a matter of life or death for Canadian patients. Furthermore, the fact remains that an entire mechanism, the CMN, was developed to mitigate barriers to accessing just two Essential Medicines for a single Neglected Disease within a regulatory system that is poorly equipped to address drugs of critical medical importance but limited commercial value. Developing individual mechanisms for individual drugs is the opposite of the systemic reforms needed.

Ivermectin

Ivermectin's story sheds light on further facets of domestic and international access to off-patent Essential Medicines for Neglected Diseases. Of late, this important antiparasitic drug has attracted considerable hype as an (unproven) treatment of COVID-19, although even Merck, the company that developed ivermectin, has cautioned against its use for this purpose.¹⁶² However, this should not overshadow its vital contributions to global health elsewhere. In 2011, Ōmura co-authored an article – perhaps not particularly modestly, but with some justification –

¹⁶¹ Guilin has been used in Canada as an alternate source to Walter Reed for a couple of years; informally, the author has been told that the CMN has indeed shifted towards this product and away from Walter Reed since the FDA approval, but formal documentation of an explicit shift is lacking. See e.g., Canadian Malaria Network, "Introduction to the Canadian Malaria Network" (April 2019), online: <https://src.healthpei.ca/sites/src.healthpei.ca/files/Laboratory%20Services/CMN_Complete_Malaria_Package.pdf>.

¹⁶² Merck & Co, "Merck Statement on Ivermectin use During the COVID-19 Pandemic", (4 February 2021), online: <<https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/>>. Merck & Co., Inc. is known as MSD outside of the United States and Canada; for ease of reference, this paper uses Merck. An in-depth study of the broader evidentiary base (or lack thereof) for ivermectin and COVID-19 is beyond the scope of this paper; however, later studies have consistently been unfavourable. See e.g., Reis, Gilmar et al., "Effect of Early Treatment with Ivermectin among Patients with Covid-19" (2022) *N Engl J Med* NEJMoa2115869, online: <<http://www.nejm.org/doi/10.1056/NEJMoa2115869>>.

highlighting ivermectin as one of the rare medicines, like aspirin and penicillin, worthy of being called a “wonder drug”, a term that might describe what an Essential Medicine aspires to be.¹⁶³ As the article notes, it is effective, safe, well-tolerated and easily administered for a range of Neglected Diseases, from those tackled via major public health campaigns like onchocerciasis (river blindness) and lymphatic filariasis (the cause of elephantiasis), to other less renowned – as Neglected Diseases go – but equally unpleasant internal parasites.¹⁶⁴ It currently has eight indications on the WHO MEML.¹⁶⁵ Ongoing research has suggested other potential uses including the prevention of malaria transmission.¹⁶⁶

Oral ivermectin tablets, of the kind used throughout much of the world for decades, were finally approved in Canada in the fall of 2018, just over three years after the Nobel Prize announcement.¹⁶⁷ Until this point, it had not been approved for human use, despite years of advocacy by Canadian physicians and entreaties from Health Canada.¹⁶⁸ The Nobel Prize and the drug’s place on the WHO MEML are both cited in Merck’s 2018 press release announcing the drug’s approval in Canada;

¹⁶³ Crump, Andy & Satoshi Ōmura. “Ivermectin, ‘wonder drug’ from Japan: the human use perspective” (2011) 87:2 Proc Jpn Acad, Ser B, Phys Biol Sci 13–28.

¹⁶⁴ Given ivermectin is generally a safe drug, it should be noted that recent media reports of toxicity in adults self-medicating with ivermectin for COVID-19 seem to have often involved extremely high doses, well beyond normal usage, including veterinary formulations. For example, the US CDC issued a warning in August 2021 following numerous reports of calls to poison control. US Centers for Disease Prevention and Control, “Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19” (26 August 2021), online: <<https://emergency.cdc.gov/han/2021/han00449.asp>>. For safety under normal conditions see e.g., Guzzo, CA et al., “Safety, Tolerability, and Pharmacokinetics of Escalating High Doses of Ivermectin in Healthy Adult Subjects” (2002) 42:10 Journal of Clinical Pharmacology 1122–1133, online: <<http://doi.wiley.com/10.1177/009127002401382731>>.

¹⁶⁵ Treatment of onchocerciasis, lymphatic filariasis, strongyloidiasis, trichuriasis, ascariasis, ancylostomiasis, hookworm diseases and scabies.

¹⁶⁶ Foy, Brian D et al. “Efficacy and risk of harms of repeat ivermectin mass drug administrations for control of malaria (RIMDAMAL): a cluster-randomised trial” (2019) 393:10180 The Lancet 1517–1526, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673618323213>>; Slater, Hannah C et al. “Ivermectin as a novel complementary malaria control tool to reduce incidence and prevalence: a modelling study” (2020) 20:4 The Lancet Infectious Diseases 498–508, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1473309919306334>>.

¹⁶⁷ The approved Canadian indications are intestinal strongyloidiasis and onchocerciasis; other WHO MEML-listed indications are off-label in Canada. A topical cream containing ivermectin for treatment of rosacea, produced by a different company, was approved in Canada in 2015.

¹⁶⁸ Houston, Adam R et al., “Reforming Canada’s Special Access Programme (SAP) to improve access to off-patent essential medicines” (2018) 3:2 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 100–107, online: <<http://jammi.utpjournals.press/doi/10.3138/jammi.2018.01.04>>.

that press release also highlights how the approval “comes as global rates of migration and travel put growing numbers of Canadians at risk of parasitic infection”.¹⁶⁹ Absent from the press release is any explanation for why Merck had chosen not to make any efforts to bring this drug to Canada at any time during the previous three decades, despite requests for it to do so.

As with artemisinin, Canadian guidelines for Neglected Diseases such as the parasitic infection strongyloidiasis have long recommended ivermectin as appropriate treatment, even while directly acknowledging difficulties (prior to its approval) in accessing it in Canada.¹⁷⁰ Similarly, ivermectin’s long absence from the formal market was not merely an inconvenience, but a danger to patients. The specifics of delays in access to ivermectin will be revisited in discussion of the SAP; for the moment, consider the expert commentary that reacted to ivermectin’s belated Canadian approval by noting how previously the “combination of lack of access to ivermectin, increasing immigration from high-risk countries and the ever-expanding use of immunosuppressing medicines, culminated in frequent cases of death due to ‘hyperinfection’ strongyloidiasis across Canada”.¹⁷¹ Strongyloidiasis is, once again, just one of the conditions ivermectin is used to treat.

There are further elements to the ivermectin story which have a bearing on the broader issue of access to off-patent Essential Medicines for Neglected Diseases. One is that, in contrast to human access, ivermectin has long been available, in a range of formulations and from a variety of companies, for veterinary use in Canada. In fact, ivermectin was initially commercialized by Merck as a

¹⁶⁹ Merck Canada Inc, “Health Canada Approves Merck’s STROMECTOL™ (ivermectin) for the Treatment of Intestinal Strongyloidiasis and Onchocerciasis”, (11 September 2018), online: <<https://www.newswire.ca/news-releases/health-canada-approves-mercks-stromectol-ivermectin-for-the-treatment-of-intestinal-strongyloidiasis-and-onchocerciasis-692934221.html>>.

¹⁷⁰ Boggild, AK et al. “CATMAT statement on disseminated strongyloidiasis: Prevention, assessment and management guidelines” (2016) 42:1 Canada Communicable Disease Report 12–19, online: <https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/publicat/ccdr-rmtc/16vol42/dr-rm42-1/assets/pdf/16vol42_1_ar-03-eng.pdf>. Strongyloidiasis has been called “the most neglected of the neglected tropical diseases”. Olsen, Annette et al., “Strongyloidiasis--the most neglected of the neglected tropical diseases?” (2009) 103:10 Trans R Soc Trop Med Hyg 967–972.

¹⁷¹ Boggild, Andrea & Antoine Corbeil. “Hot topics in tropical medicine: Approval of Ivermectin by Health Canada”, (12 April 2019), online: *BMC Blog Network - On Medicine* <<https://blogs.biomedcentral.com/on-medicine/2019/04/12/hot-topics-tropical-medicine-approval-ivermectin-health-canada/>>.

veterinary drug, and proved to be a very profitable one. The initial Ivomec formulation for cattle became the most successful veterinary drug of the 1980s.¹⁷² For over twenty years it maintained blockbuster status, with global sales over one billion dollars (US) annually.¹⁷³ As such, this Nobel Prize-winning drug did not originate as part of a quest to cure parasitic diseases in some of the world's poorest communities, but as an afterthought for a very profitable veterinary drug. Its marketing for veterinary applications in markets where it is absent for human use underlines the commercial considerations behind its availability. It also raises an important point about the overlap between human and animal health. As zoonotic diseases, and the broader relationship between human and animal health, gain traction through approaches such as One Health, the links shared by man and beast when it comes to pharmaceuticals deserve further attention.¹⁷⁴ Antimicrobial resistance will be revisited elsewhere in this thesis, but other areas of overlap between the human and veterinary pharmaceutical markets – including for underlying Active Pharmaceutical Ingredients (APIs) shared by these different formulations – are worthy of further study.¹⁷⁵

Another important issue aptly illustrated by ivermectin, and one that will also receive further attention later in this thesis, is that of sustainable global access. Ivermectin occupies a strange place: Even during the decades it was unavailable in Canada for commercial reasons, billions of doses were being donated, rather than sold, by its manufacturer for human use worldwide. Beyond its own medical

¹⁷² Collins, Kimberly Layne. "Profitable Gifts: A History of the Merck Mectizan Donation Program and Its Implications for International Health" (2004) 47:1 *Perspectives in Biology and Medicine* 100–109, online:

<http://muse.jhu.edu/content/crossref/journals/perspectives_in_biology_and_medicine/v047/47_1collins.html>.

¹⁷³ Crump, Andy & Satoshi Ōmura. "Ivermectin, 'wonder drug' from Japan: the human use perspective" (2011) 87:2 *Proc Jpn Acad, Ser B, Phys Biol Sci* 13–28.

¹⁷⁴ For more on One Health see e.g., World Health Organization, "One Health" (2020), online: <<http://www.who.int/features/qa/one-health/en/>>; Fisman, David N & Kevin B Laupland, "The 'One Health' paradigm: Time for infectious diseases clinicians to take note?" (2010) 21:3 *Can J Infect Dis Med Microbiol* 111–114.

¹⁷⁵ The issue of antimicrobial resistance is given additional wrinkles in a One Health context. See e.g., Tang, Karen L et al., "Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis" (2017) 1:8 *The Lancet Planetary Health* e316–e327, online: <<https://linkinghub.elsevier.com/retrieve/pii/S2542519617301419>>.

importance, ivermectin was the spark that ignited one of the biggest shifts in access to Essential Medicines for Neglected Diseases at the global level: large-scale, long-term corporate donation for the eradication of a Neglected Disease in LMICs. This saga offers further intriguing insights into the commercial considerations behind Essential Medicines for Neglected Diseases. Merck began its ivermectin donation program in 1987, declaring that it would donate the drug free of charge, as much as needed and for as long as needed, for the treatment of the Neglected Disease onchocerciasis; by 1998, the donation program had been expanded to a second Neglected Disease, lymphatic filariasis.¹⁷⁶ By 2021, over four billion doses had been donated.¹⁷⁷ While underwritten by lucrative veterinary sales, this pioneering drug donation program remains one of the largest donation programs by a pharmaceutical company, and its positive public health impact should certainly be acknowledged. What is more, it has also inspired similar mass donation campaigns by other pharmaceutical companies.¹⁷⁸ At the same time, the story is more complex than a simple act of good corporate citizenship, and carries with it implications for future access.

First, in this case, philanthropy was not the original goal behind ivermectin's redevelopment of its blockbuster veterinary drug into one for human use. Merck initially viewed ivermectin as a potential commercial product for treatment of individual patients, in contrast to other (non-commercial) actors who saw it as a potential population-level public health tool to stop the ongoing transmission of parasites.¹⁷⁹ However, as is often the case with drugs for Neglected Diseases, Merck could not see a way towards making a treatment for river blindness profitable; echoing a theme seen throughout this thesis, people with river blindness simply

¹⁷⁶ Merck & Co. *Press Release - Merck Commemorates 30 Years of MECTIZAN® Donation Program Progress* (Merck & Co., 2017), online <<https://investors.merck.com/news/press-release-details/2017/Merck-Commemorates-30-Years-of-MECTIZAN-Donation-Program-Progress/default.aspx>>.

¹⁷⁷ Merck, "Over 30 Years: The Mectizan® Donation Program" (6 January 2021), online: <<https://www.merck.com/stories/mectizan/>>.

¹⁷⁸ Like GlaxoSmithKline (GSK) and albendazole, a company and a drug discussed in more detail elsewhere.

¹⁷⁹ Crump, Andy & Satoshi Ōmura. "Ivermectin, 'wonder drug' from Japan: the human use perspective" (2011) 87:2 *Proc Jpn Acad, Ser B, Phys Biol Sci* 13–28.

aren't a lucrative market.¹⁸⁰ It was those other partners, such as the WHO's Special Programme for Research & Training in Tropical Diseases (TDR), who actually funded much of the community-based research, while Merck pursued registration of the drug for individual patients, first obtaining it in France.¹⁸¹ Only after Merck was unable to find a donor to pay for the drug did the company move forward with donating it.¹⁸²

Second, despite some undeniable successes thus far, it is also unclear how sustainable such mass donation programs will be in the future. The current approach, while yielding tangible global health benefits, also puts programs at the mercy of the decisions of corporate donors. Donations can also be a disincentive to developing sustainable alternative sources of the drug, be those sources commercial, state-owned, or even non-profit. They may even drive treatment decisions for Neglected Diseases, for instance in cases where one Essential Medicine is donated while another must be purchased.¹⁸³ Concerns about the potential impacts of accepting corporate donations, rather than encouraging sustainable long-term production by multiple producers, have led to situations where humanitarian organizations have declined corporate donations of Essential Medicines in favour of purchasing generic versions to foster competition.¹⁸⁴ For similar reasons, Lin and Addiss caution, "Donations should not be relied upon as an

¹⁸⁰ Collins, Kimberly Layne. "Profitable Gifts: A History of the Merck Mectizan Donation Program and Its Implications for International Health" (2004) 47:1 *Perspectives in Biology and Medicine* 100–109, online: <http://muse.jhu.edu/content/crossref/journals/perspectives_in_biology_and_medicine/v047/47.1collins.html>.

¹⁸¹ Crump, Andy & Satoshi Ōmura. "Ivermectin, 'wonder drug' from Japan: the human use perspective" (2011) 87:2 *Proc Jpn Acad, Ser B, Phys Biol Sci* 13–28.

¹⁸² Collins, Kimberly Layne. "Profitable Gifts: A History of the Merck Mectizan Donation Program and Its Implications for International Health" (2004) 47:1 *Perspectives in Biology and Medicine* 100–109, online: <http://muse.jhu.edu/content/crossref/journals/perspectives_in_biology_and_medicine/v047/47.1collins.html>.

¹⁸³ See e.g., Manne, Jennifer M et al. "Barriers to Treatment Access for Chagas Disease in Mexico" (2013) 7:10 *PLoS Negl Trop Dis* e2488, online: <<https://dx.plos.org/10.1371/journal.pntd.0002488>>.

¹⁸⁴ See e.g., Smith, James, "When free is not fair: the case of vaccine donations" (2017) 17:2 *The Lancet Infectious Diseases* 128–130, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1473309917300087>>.

indefinite global health solution".¹⁸⁵ This is especially important, they argue, for mass donation programs for Neglected Diseases that cannot be eradicated through mass administration alone:

Epidemiological characteristics for lymphatic filariasis, onchocerciasis, and trachoma make them amenable to elimination through preventive chemotherapy as the primary intervention. These programmes have clear disease elimination goals, with defined endpoints and with a foreseeable end to the need for donated drugs and programmatic support. By contrast, preventive chemotherapy alone is unlikely to eliminate STH [soil-transmitted helminths]. Long-term STH control is a probable scenario, and indefinite dependence on annual donation of more than 1 billion treatments has both practical and ethical implications.¹⁸⁶

As such, while this thesis is far from advocating for ending mass donation programs in LMICs, real consideration should be given to their overall role in ensuring sustainable global access to Essential Medicines. The consequences of both fickle corporate decision-making and unsustainable single-source manufacturers both figure into the story unfurling in the coming pages. Donations also have implications for Canada. For one, the provision of a drug for free can actually serve to reinforce access barriers in HICs as well; after all, it's harder for the government, or members of the public, to put pressure on a company to bring a drug to market when that company can point to the fact it is already providing the drug for free, via the government's own less than ideal mechanism. For another, market approval can bring its own challenges. Prior to its approval in Canada, when it was obtainable only via the SAP, ivermectin was provided for free by Merck in the limited quantities that were accessed. While its formal approval carries multiple

¹⁸⁵ Lin, William M & David G Addiss. "Sustainable access to deworming drugs in a changing landscape" (2018) 18:12 The Lancet Infectious Diseases e395–e398, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1473309918303517>>.

¹⁸⁶ Lin, William M & David G Addiss. "Sustainable access to deworming drugs in a changing landscape" (2018) 18:12 The Lancet Infectious Diseases e395–e398, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1473309918303517>>.

benefits, it also now comes at a cost of \$7 per pill, potentially a burden for patients without drug coverage.¹⁸⁷ This underscores that market entry is itself not a complete solution; other issues, from market sustainability to public and private drug coverage, must also be considered. Finally, it should be noted that even during the years that ivermectin was not available for human use in Canada, Canada was actively promoting access to it in other countries.¹⁸⁸ Indeed, for a long period Canada's contribution to the African Regional Trust Fund for River Blindness was only slightly less than Merck's.¹⁸⁹ As such, it marks yet another instance where Canada's domestic and international policies promoting access to Essential Medicines have failed to align.

The Interagency Emergency Health Kit

The drugs highlighted so far are all decades-old Essential Medicines, whose use abroad has been generously supported by Canada, and which have been included in Canada's own treatment standards despite being unavailable domestically. They also fit within a larger pattern of off-patent Essential Medicines for Neglected Diseases being absent from Canada. As a final illustration, consider the Interagency Emergency Health Kit ("Interagency Kit"), one of a number of international health initiatives that use the WHO MEML as an anchor point.¹⁹⁰ The Interagency Emergency Health Kit, as its name suggests, is designed as a toolkit for responding to health needs during emergencies such as natural disasters or other

¹⁸⁷ Boggild, Andrea & Antoine Corbeil. "Hot topics in tropical medicine: Approval of Ivermectin by Health Canada", (12 April 2019), online: *BMC Blog Network - On Medicine* <<https://blogs.biomedcentral.com/on-medicine/2019/04/12/hot-topics-tropical-medicine-approval-ivermectin-health-canada/>>.

¹⁸⁸ Global Affairs Canada. *Project profile — African Program for Onchocerciasis Control - Phase III* (Government of Canada, n/d), online <<https://w05.international.gc.ca/projectbrowser-banqueprojets/project-projet/details/a033538001>>.

¹⁸⁹ Bundy, Donald A P et al. "Investing in Onchocerciasis Control: Financial Management of the African Programme for Onchocerciasis Control (APOC)" (2015) 9:5 PLoS Negl Trop Dis e0003508, online: <<https://dx.plos.org/10.1371/journal.pntd.0003508>>.

¹⁹⁰ Some of the research conducted for this sub-section was previously published as Houston, Adam R & Jason W Nickerson, "Lessons from the Interagency Emergency Health Kit for access to essential medicines in Canada" (2019) 4:1 Int J Humanitarian Action 2, online: <<https://jhumanitarianaction.springeropen.com/articles/10.1186/s41018-019-0049-8>>.

humanitarian crises.¹⁹¹ Particularly in its basic form, it offers one of the most extreme examples of the WHO MEML being adapted for a particular purpose. Demonstrating the widespread acceptance of the Essential Medicines concept, it is a collaborative effort between a number of UN agencies (World Health Organization, United Nations Children's Fund, United Nations High Commissioner for Refugees, United Nations Population Fund) and leading international NGOs (International Committee of the Red Cross International Federation of the Red Cross and Red Crescent Societies, Médecins Sans Frontières).¹⁹² It is a longstanding effort, with the first edition dating back to 1990; it builds upon an even earlier tool, the WHO Emergency Health Kit.¹⁹³

The Interagency Kit includes both a basic unit and a larger supplementary unit, both designed to serve 10,000 people for 3 months.¹⁹⁴ The basic unit does not only contain Essential Medicines; it also includes rudimentary tools for providing health services in an emergency, including scissors, soap, bandages, and cotton wool, as well as notebooks and pens for record keeping. The results resemble a first-aid kit on a massive scale; echoing this, the pharmaceutical components could also be considered the first-aid kit to the WHO MEML's pharmacy. As such, the basic unit of the Interagency Kit boils down the over 400 drugs of the MEML to just 14.¹⁹⁵ Shockingly, of the 14 drugs included in the most recent iteration of the basic Interagency Kit, only 10 have marketing approval for human use in Canada. Those 14 drugs include basic medicines familiar to any Canadian medicine cabinet, like

¹⁹¹ WHO Expert Committee on the Use of Essential Drugs, ed. *The interagency health kit 2017: medicines and medical devices for 10 000 people for approximately three months* (Geneva, 2019), online: <<https://apps.who.int/iris/bitstream/handle/10665/279428/9789241515221-eng.pdf>>.

¹⁹² WHO Expert Committee on the Use of Essential Drugs, ed. *The interagency health kit 2017: medicines and medical devices for 10 000 people for approximately three months* (Geneva, 2019), online: <<https://apps.who.int/iris/bitstream/handle/10665/279428/9789241515221-eng.pdf>>.

¹⁹³ The WHO Emergency Health Kit was itself originally developed by WHO Emergency Relief Operations in collaboration with the Office of the United Nations High Commissioner for Refugees (UNHCR) and the London School of Hygiene and Tropical Medicine. World Health Organization, ed, *WHO emergency health kit: standard drugs and clinic equipment for 10,000 persons for 3 months* (Geneva : 1984).

¹⁹⁴ WHO Expert Committee on the Use of Essential Drugs, ed. *The interagency health kit 2017: medicines and medical devices for 10 000 people for approximately three months* (Geneva, 2019), online: <<https://apps.who.int/iris/bitstream/handle/10665/279428/9789241515221-eng.pdf>>.

¹⁹⁵ WHO Expert Committee on the Use of Essential Drugs, ed. *The interagency health kit 2017: medicines and medical devices for 10 000 people for approximately three months* (Geneva, 2019), online: <<https://apps.who.int/iris/bitstream/handle/10665/279428/9789241515221-eng.pdf>>.

acetaminophen (paracetamol) and ibuprofen. The corollary to this is that four drugs considered by multiple key international health organizations to be as basic as acetaminophen and ibuprofen are not formally available in Canada. Not only are all four of these absent drugs found on the WHO MEML, they are all indicated for the treatment of Neglected Diseases.

This state of affairs offers several points of reflection on the universality of Essential Medicines in a national context. While Canada is not in the midst of any emergency requiring widespread distribution of the Interagency Kit by the international community, it is also difficult to believe it is so far removed from global health priorities that four out of fourteen of the most basic Essential Medicines worldwide are not merely absent from Canada's (as-yet nonexistent) EML, but simply absent from Canada entirely. Sometimes an alternative treatment is available. For instance, rather than the benzyl benzoate lotion found in the Interagency Kit, the usual treatment for lice and scabies (a Neglected Disease) in Canada is permethrin (itself also on the WHO MEML).¹⁹⁶ Similarly, tetracycline ointment is used for a range of eye infections, including the Neglected Disease trachoma. For some conditions treated with tetracycline ointment, other treatments may be available, but may not always be the most suitable.¹⁹⁷ Even where alternatives exist, however, the absence of these Essential Medicines from the Canadian market can have other impacts. One is cost. The Canadian Pediatric Society, in their position statement on scabies, notes that benzyl benzoate is widely used elsewhere, and offers high efficacy at a lower price.¹⁹⁸ It isn't necessarily better than permethrin, but it is cheaper. Cost is not the only potential consideration when it comes to drugs, of course. Another is simply ensuring that alternatives are available in case they are needed. Shortages of other options that are formally available for treating eye infections, like erythromycin, have been

¹⁹⁶ Banerji, Anna. "Scabies" (2015) 20:7 Paediatrics & Child Health 395–398, online: <<https://academic.oup.com/pch/article-lookup/doi/10.1093/pch/20.7.395>>.

¹⁹⁷ See e.g., Moore, Dorothy L, Noni E MacDonald, & Canadian Paediatric Society, Infectious Diseases and Immunization Committee, "Preventing ophthalmia neonatorum" (2015) 26:3 Can J Infect Dis Med Microbiol 122–125.

¹⁹⁸ Banerji, Anna. "Scabies" (2015) 20:7 Paediatrics & Child Health 395–398, online: <<https://academic.oup.com/pch/article-lookup/doi/10.1093/pch/20.7.395>>.

reported in recent years, underscoring the potential value of having multiple options available.

The third missing Essential Medicine is artemether/lumefantrine, the combination medication that was highlighted earlier as the drug of choice for treating uncomplicated *P. falciparum* malaria.¹⁹⁹ The last of the four drugs in the Interagency Kit that remains absent from Canada is albendazole, a drug introduced in the opening pages of this thesis, and the gold standard treatment for a range of parasitic diseases. Like ivermectin, it is a workhorse of global health, with nine indications on the WHO MEML; unlike ivermectin, it still has not been approved for human use in Canada (cattle, by contrast, do have the option). Nonetheless, albendazole is relied upon by Canadian physicians for treating numerous diseases. Some parasitic Neglected Diseases may be relatively uncommon in Canadian-born populations, but are more frequent in populations who immigrate to Canada from endemic countries. This is not a novel issue; for instance, it was identified as a concern in Southeast Asian refugees who came to Canada in the early 1980s.²⁰⁰ Clinical guidelines used in Canada for screening and treating such parasitic Neglected Diseases in refugee and immigrant populations recommend the use of, depending on the condition, either albendazole or ivermectin or both, even though both drugs were unavailable in Canada at the time that key guidelines were crafted.²⁰¹ As such, these guidelines specifically include notations such as “if patients require treatment for strongyloidiasis with ivermectin or albendazole, these drugs must be obtained through Health Canada’s Special Access Programme”.²⁰² At other times, the SAP is not explicitly mentioned in official Canadian sources, even where it would be the only option for access. For instance, a

¹⁹⁹ World Health Organization & Global Malaria Programme. *Guidelines for the treatment of malaria*. (2015). As noted earlier, *P. falciparum* is the deadliest kind of malaria.

²⁰⁰ Asundi, Archana et al. “Prevalence of strongyloidiasis and schistosomiasis among migrants: a systematic review and meta-analysis” (2019) 7:2 The Lancet Global Health e236–e248, online: <<https://linkinghub.elsevier.com/retrieve/pii/S2214109X1830490X>>.

²⁰¹ Pottie, K et al. “Evidence-based clinical guidelines for immigrants and refugees” (2011) 183:12 Canadian Medical Association Journal E824–E925, online: <<http://www.cmaj.ca/cgi/doi/10.1503/cmaj.090313>>.

²⁰² Pottie, K et al. “Evidence-based clinical guidelines for immigrants and refugees” (2011) 183:12 Canadian Medical Association Journal E824–E925, online: <<http://www.cmaj.ca/cgi/doi/10.1503/cmaj.090313>>.

Government of Canada Pathogen Safety Data Sheet on the Neglected Disease lymphatic filariasis lists three drugs – all Essential Medicines – as appropriate drug therapy; at the time the data sheet was written, ivermectin was not yet marketed, albendazole remains unmarketed to this day, and the third, diethylcarbamazine, had previously been marketed but was discontinued in Canada in the year 2000.²⁰³

It must be emphasized that such antiparasitic drugs are crucial for a wide range of Neglected Diseases, some of which are increasingly common in Canada. Another example is neurocysticercosis, a serious condition caused by a parasite of pigs (*Taenia solium*).²⁰⁴ Other HICs like the United States have also seen an increase in neurocysticercosis cases in recent decades, similarly driven by increased migration and travel.²⁰⁵ Part of the treatment involves albendazole; that this drug has only been available to treating physicians in Canada via the Special Access Programme is noted in the scientific literature.²⁰⁶ As a further example, the past few years have seen the emergence of domestically acquired human cases of the parasitic Neglected Disease *Echinococcus multilocularis*, an otherwise fatal condition that, somewhat unusually for a Neglected Disease, may require lifetime treatment.²⁰⁷ Previously found only in Europe, the disease appears to have become

²⁰³ Health Canada, “Pathogen Safety Data Sheets: Infectious Substances – *Wuchereria bancrofti*” (18 February 2011), online: <https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/wuchereria-bancrofti.html>

²⁰⁴ Del Brutto, Oscar H, “A review of cases of human cysticercosis in Canada” (2012) 39:3 Can J Neurol Sci 319–322; see also more broadly Mewara, Abhishek, Kapil Goyal & Rakesh Sehgal, “Neurocysticercosis: A disease of neglect” (2013) 3:2 Trop Parasitol 106–113.

²⁰⁵ Wallin, M T & J F Kurtzke, “Neurocysticercosis in the United States: Review of an important emerging infection” (2004) 63:9 Neurology 1559–1564, online: <http://www.neurology.org/cgi/doi/10.1212/01.WNL.0000142979.98182.FF>.

²⁰⁶ See e.g., Burneo, J G et al., “Neurocysticercosis in a patient in Canada” (2009) 180:6 Canadian Medical Association Journal 639–642, online: <http://www.cma.ca/cgi/doi/10.1503/cmaj.081452>; for broader treatment discussion see White, A Clinton et al., “Diagnosis and Treatment of Neurocysticercosis: 2017 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH)” (2018) 66:8 Clinical Infectious Diseases e49–e75, online: <https://academic.oup.com/cid/article/66/8/e49/4885412>.

²⁰⁷ Houston, Stan et al., “Epidemiological and Clinical Characteristics of Alveolar Echinococcosis: An Emerging Infectious Disease in Alberta, Canada” (2021) The American Journal of Tropical Medicine and Hygiene, online: <https://www.ajtmh.org/view/journals/tpmd/aop/article-10.4269-ajtmh.20-1577/article-10.4269-ajtmh.20-1577.xml>. See also, more broadly Silva, António Menezes da, “Human echinococcosis: a neglected disease” (2010) 2010 Gastroenterol Res Pract 583297.

established in some wildlife populations such as coyotes on the prairies.²⁰⁸ The recommended treatment? Albendazole.

Access to Essential Medicines for Neglected Diseases has ultimately failed to garner the same degree of interest, whether from the media or from policymakers, as access to medicines for other small populations such as Rare Diseases (an issue that will be explored later on). The absence of these basic Essential Medicines from the Canadian market has at best attracted sporadic media coverage in recent years.²⁰⁹ For every story that makes the news, there are multiple drugs that are unavailable, and multiple patients who face barriers to access; furthermore, what limited attention there has been has yet to tip the scales towards regulatory reforms aiding their path to market. Nonetheless, the fact that Canada is a particular outlier in relation to albendazole is highlighted in a further incident, which somewhat unusually received international news coverage. This story involves two Canadian tourists who contracted hookworm in the Dominican Republic. In Canada, the inability to access treatment – albendazole – was a major part of the story.²¹⁰ In foreign coverage, sometimes the inability to access the drug in Canada was remarked upon, and contrasted with ready local access.²¹¹ At other times, the issue of Canadian access to treatment was not picked up on at all, with the emphasis placed on how cheap and easily accessible albendazole is.²¹² The nonchalant omission of the Canadian access issue in these latter stories underscores how arbitrary the absence of these drugs from Canada – despite the

²⁰⁸ Massolo, Alessandro et al. "European *Echinococcus multilocularis* Identified in Patients in Canada" (2019) 381:4 N Engl J Med 384–385, online: <<http://www.nejm.org/doi/10.1056/NEJMc1814975>>.

²⁰⁹ For two examples, both quoting this author, see Fournier, Ariel. "The life-saving medicine she needs is cheap, common and unavailable in Canadian pharmacies", *CBC News* (30 January 2020), online: <<https://www.cbc.ca/news/canada/edmonton/parasite-survivor-access-to-drugs-1.5446030>>; Grant, Kelly. "Why world-beating tropical drugs are so hard to get in Canada", *Globe and Mail* (2 January 2017), online: <<https://www.theglobeandmail.com/news/national/why-world-beating-tropical-drugs-are-so-hard-to-get-incanada/article33469954/>>.

²¹⁰ Chen, Dalson. "Caribbean vacation turns into parasite nightmare for Windsor couple", *Windsor Star* (26 January 2018), online: <<https://windsorstar.com/news/local-news/caribbean-vacation-turns-into-parasite-nightmare-for-windsor-couple>>.

²¹¹ Lieber, Mark. "Couple finds worms in their feet after a beach vacation", *CNN* (2 February 2018), online: <<https://www.cnn.com/2018/01/30/health/worms-feet-vacation/index.html>>.

²¹² Kim, Soo. "Travellers warned after barefoot paradise beach walk earns couple parasitic foot infection", *The Telegraph* (28 January 2018), online: <<https://www.telegraph.co.uk/travel/news/hookworm-risks-barefoot-beach-holidays/>>.

presence of patients who need them – really is. Together, the examples discussed in this chapter thus far provide some context for different aspects of the access issue. However, this is only a taste of the more than 30 medicines for Neglected Diseases currently found on the WHO MEML that are currently unavailable in Canada, a larger number of which are outlined in **Table 2**.²¹³

²¹³ Table 2 is derived from the 22nd WHO MEML (2021) and the Health Canada Drug Product Database as of April 2022.

Table 2: Selected Off-Patent Essential Medicines for Neglected Diseases absent from the Canadian market

Essential Medicine	WHO MEML Indication	Canadian Market Status (for human use)
albendazole	Filariasis; Echinococcosis; Ascariasis; Enterobiasis; Trichuriasis; Hookworm diseases; Cysticercosis.	Never
amodiaquine	Malaria (<i>P. falciparum</i>) curative	Never
amodiaquine + sulfadoxine + pyrimethamine	Malaria chemoprophylaxis	Never
artemether	Malaria (<i>P. falciparum</i>) curative	Never
artemether + lumefantrine	Malaria (<i>P. falciparum</i>) curative	Never
artesunate	Malaria (<i>P. falciparum</i>) curative	Never
artesunate + amodiaquine	Malaria (<i>P. falciparum</i>) curative	Never
artesunate + mefloquine	Malaria (<i>P. falciparum</i>) curative	Never
artesunate + pyronaridine tetraphosphate	Malaria (<i>P. falciparum</i> , <i>P. vivax</i>) curative	Never
benznidazole	American trypanosomiasis	Never
benzyl benzoate	Scabies	Never
chloroquine	Malaria (<i>P. vivax</i>) curative; Malaria (<i>P. vivax</i> , <i>P. ovale</i> , <i>P. malariae</i>) chemoprophylaxis; rheumatoid arthritis	Last source discontinued 2021
clofazimine	Multidrug-resistant tuberculosis; leprosy	Never
cycloserine	Multidrug-resistant tuberculosis	Last source discontinued 1997
diphtheria antitoxin	Diphtheria	Last source discontinued 2000
diethylcarbamazine	Lymphatic filariasis	Last source discontinued 2000
dihydroartemisinin + piperazine phosphate	Malaria (<i>P. falciparum</i>) curative	Never
dioxanide	Amoebiasis	Never
eflornithine	African trypanosomiasis (sleeping sickness) (2 nd Stage)	Never* (*except skin cream, marketed 2005)
ethionamide	Multidrug-resistant tuberculosis	Never
flucytosine	Cryptococcosis	Never
ivermectin	Strongyloidiasis; Ascariasis; Trichuriasis; Hookworm diseases; Ancylostomiasis; Onchocerciasis; Lymphatic filariasis; Scabies	First marketed 2018 (except rosacea cream, marketed 2015)
levamisole	Ascariasis	Last source discontinued 2005
melarsoprol	African trypanosomiasis (2 nd stage)	Never
miltefosine	Leishmaniasis (visceral, mucocutaneous, cutaneous)	Never
niclosamide	Tape worm (Hymenolepiasis, Diphylobothriasis); Taeniasis due to <i>Taenia saginata</i> & <i>Taenia solium</i>	Never
nifurtimox	African trypanosomiasis; American trypanosomiasis	Never
oxamniquine	Schistosomiasis	Never
p-aminosalicylic acid	Multidrug-resistant tuberculosis	Never
pyrimethamine	Toxoplasmosis	Last source discontinued 2013
rifapentine	Tuberculosis, latent tuberculosis	Never
sodium stibogluconate	Leishmaniasis (visceral, mucocutaneous, cutaneous)	Never
sulfadoxine + pyrimethamine	Malaria (<i>P. falciparum</i>), curative & chemoprevention	Last source discontinued 2000
suramin sodium	African trypanosomiasis (1 st stage)	Never
triclabendazole	Fascioliasis, paragonimiasis	Never

Chapter 2: Why aren't these Essential Medicines available in Canada?

Canadian approval: A quick primer

So why aren't Essential Medicines like cycloserine, artemisinin and albendazole formally available in Canada in the first place? And why are the only options to attempt to gain access ill-fitting tools like the SAP? Before exploring the broader landscape of pharmaceutical governance in Canada, it is useful to very quickly recap how a drug reaches the Canadian market, including the crucial but oft overlooked lynchpin upon which the regulatory process depends. In brief, before any drug can be marketed, it must be approved by Health Canada, under the auspices of the Therapeutic Products Directorate. To obtain approval, a drugmaker must comply with the requirements of the *Food and Drugs Act* and the *Food and Drug Regulations*, and provide information on the drug's safety, efficacy and quality. A manufacturer first submits a New Drug Submission (NDS) for evaluation. Approval results in the issuance of a Notice of Compliance (NOC), which shows that the drug meets the required standards for use in humans.²¹⁴ This also results in issuance of a Drug Identification Number (DIN), which shows that the drug has been evaluated and authorised for marketing and sale in Canada.²¹⁵ The indications (i.e., diseases or conditions) for which the drug is approved will appear on the product's monograph (in essence, its label); the monograph will also indicate the population group(s) for which the drug has been approved, and any contra-indications (i.e., when not to use the drug).

This process requires a catalyst, however. The fact is that the regulatory process is dependent upon an interested party seeking approval. For the majority of drugs, old and new, eager market entrants mean this is never an issue. If no party is interested in selling a drug in Canada, however, the regulatory process is never initiated. Unfortunately, this has been the fate of multiple Essential Medicines for Neglected Diseases, even while they constitute the standard of care. Often, these drugs are simply not very commercially enticing. When a disease is

²¹⁴ C.08.002, *Food and Drug Regulations* (C.R.C., c. 870).

²¹⁵ C.01.014, *Food and Drug Regulations* (C.R.C., c. 870).

uncommon, the small number of patients who require a drug – especially a curative drug often needed only for a short period rather than for a lifetime – means even a modest profit per pill may not come out a winner in the accountant’s spreadsheet. This calculation may go beyond simply the profitability of serving a particular market at an affordable price; it might involve a more complex equation evaluating the cost and effort of receiving market approval, including regulatory fees, and subsequently the expenses of manufacturing, distributing and stocking the drug, as well as complying with other ongoing regulatory requirements. It may also involve the opportunity cost of balancing all these considerations against those for another product. One result of such commercial considerations is that an Essential Medicine may be withdrawn from the market; another is that it may never be introduced in the first place, meaning Health Canada never even has the opportunity to assess the safety, quality and efficacy of an Essential Medicine that would readily meet its standards, simply because no application is ever made. In turn, while Canada’s regulatory apparatus does have simpler, cheaper, and faster pathways to approval, these pathways are not well tailored to the drugs under discussion. For instance, if a drugmaker wishes to market a generic version of an existing approved drug, the applicant may submit an Abbreviated New Drug Submission (ANDS), a simplified and less expensive procedure.²¹⁶ However, this requires a drug already on the market to serve as a Canadian reference point; an old Essential Medicine used for decades but never formally sold in Canada will not have such a reference point, and thus is not eligible for this simpler, cheaper option even if it constitutes the standard of care. Other streamlined pathways may be available but still insufficient to tip the balance on deciding to bring a drug to market. Consider the Notice of Compliance with Conditions (NOC/c).²¹⁷ This designation is reserved for drugs addressing conditions for which no drug is presently marketed in Canada, or that show significantly improved efficacy or reduced risk over alternatives. As a pre-condition for an NOC/c, safety of the drug must be reasonably established. For an

²¹⁶ C.08.002.1, *Food and Drug Regulations* (C.R.C., c. 870).

²¹⁷ Health Canada, “Notice of Compliance with Conditions - NOC/c (Therapeutic Products)”, online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/factsheets/notice-compliance-conditions-therapeutics-products.html>>.

Essential Medicine that already serves as the standard of care, these criteria should be relatively easy to meet. The same can be said for another mechanism, the Priority Review process, for which drugs are eligible if they address a serious, life-threatening, or severely debilitating condition.²¹⁸ Once again, however, both of these tools for accelerated approval still depend upon a manufacturer's interest in applying to bring the drug to market. If the decision to enter the market is made, these more streamlined paths can be helpful; the problem is that for off-patent Essential Medicines for Neglected Diseases this decision is frequently not reached in the first place.

The dependence of the regulatory apparatus on commercial interest is thus a real issue when it comes to off-patent Essential Medicines for Neglected Diseases. It does not matter that treating a disease like DR-TB has immense benefits to both the patient and to public health if the financial benefits of bringing it to market are seen as too small. The result is that regulatory goals never actually have the opportunity to be met, even where they almost certainly would be. Particularly for a drug used for decades by millions of people taking billions of doses, like albendazole, safety and efficacy are realistically not a major concern (when used properly); for others like cycloserine, neither safety nor efficacy are optimal, but they are nonetheless known quantities. This leaves quality, which may be a genuine concern for some sources of Essential Medicines, but is nonetheless an issue that, as will be discussed, can be overcome.²¹⁹ Unfortunately, as will be seen, Canada's pharmaceutical regulatory system is premised upon protecting people by preventing access to ineffective, unsafe, or poor quality medicines, rather than protecting them by promoting access to Essential Medicines whose medical value to patients outweighs their commercial value to pharmaceutical companies.

²¹⁸ Health Canada, "Priority Review of Drug Submissions Policy", online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/policies/policy-priority-review-drug-submissions.html>>.

²¹⁹ As noted earlier, this issue is particularly salient for antimalarials. See also Brower, Vicki, "Falsified and substandard malaria drugs in Africa" (2017) 17:10 *The Lancet Infectious Diseases* 1026–1027, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1473309917305285>>.

Governing pharmaceuticals in Canada: Provincial jurisdiction over health

So how can useful but unprofitable Essential Medicines be made more accessible?

On the surface, the answer to this question threatens to get bogged down in the tangled morass of Canadian health governance. As famously stated by Justice Estey in *Schneider v. The Queen*, health “is not a matter which is subject to specific constitutional assignment but instead is an amorphous topic which can be addressed by valid federal or provincial legislation, depending in the circumstances of each case on the nature or scope of the health problem in question”.²²⁰ This remains broadly true of pharmaceuticals, where the journey between drug manufacturer and patient traverses jurisdictional lines. At the same time, as will be seen, when the key “health problem in question” is access to off-patent Essential Medicines for Neglected Diseases, many of these jurisdictional complications can be avoided.

Taking a step back for a broader overview, the regulation of pharmaceuticals themselves is not explicitly assigned under Canada’s constitutional division of powers. At first glance, one might speculate that their absence could reflect the rather primitive state of pharmaceutical regulation (and for that matter the primitive state of pharmaceuticals to be regulated) at the time these powers were divided up; this would not be the first time that constitutional drafters of the 19th Century failed to anticipate the innovations of the 20th and 21st Centuries. First glances can be deceiving, however; as discussed shortly, pharmaceutical regulation was in fact duly taken up within Canada’s first decade of existence, and the jurisdictional question raised and resolved. While the underlying goals of pharmaceutical regulation have evolved considerably in the interim – it would be nearly a century after Confederation before the full regulatory scope of safety, efficacy and quality was embraced – the authority underpinning the issues at the core of this thesis has not.

Nevertheless, important aspects of pharmaceutical governance are to be found on both sides of the division of powers and should be acknowledged. Numerous aspects of health, including many of the areas most concerned with

²²⁰ *Schneider v. The Queen*, [1982] 2 S.C.R. 112, p. 142. (Concurring judgement).

pharmaceuticals, fall within provincial jurisdiction. Some of this provincial jurisdiction over health is explicit; for instance, hospitals and similar institutions, where many drugs are dispensed and consumed, are within provincial jurisdiction.²²¹ Other aspects of jurisdiction over healthcare have been drawn from general provincial jurisdiction over “property and civil rights”.²²² This includes the regulation of health professionals, an area that includes physicians and pharmacists and as such has consequences for access to Essential Medicines for Neglected Diseases that will receive particular attention later on. Similarly, residual power over “matters of a strictly local or private nature” has also been interpreted as granting extensive provincial jurisdiction over healthcare.²²³ This too has been affirmed by the Supreme Court of Canada.²²⁴ These aforementioned powers also give provinces jurisdiction over insurance programs.²²⁵ One important consequence is that provinces also establish their own lists of important medicines: provincial formularies of drugs, with which they control reimbursement under provincial insurance plans. In practice, these different provincial formularies lead to variable access to different drugs across the country.²²⁶ This inequity between provinces itself illustrates the value of a shared point of reference like a Canadian EML or formulary.

Such inequities apply to unmarketed drugs as well, even as these drugs raise further access challenges. While some drugs accessed via the SAP may be provided by the manufacturer for free, others can be quite expensive. Different provinces have different policies regarding reimbursement of unmarketed drugs; these policies have themselves evolved over time.²²⁷ Today, provinces generally have

²²¹ The “establishment, maintenance, and management of hospitals, asylums, charities, and eleemosynary institutions” per s.92(7) of *The Constitution Act, 1867*.

²²² S.92(13), *The Constitution Act, 1867*. (UK), 30 & 31 Victoria, c 3.

²²³ S.92(16), *The Constitution Act, 1867* (UK), 30 & 31 Victoria, c 3.

²²⁴ See e.g., *Reference re Assisted Human Reproduction Act*, 2010 SCC 61, [2010] 3 S.C.R. 457.

²²⁵ See *Reference re legislative jurisdiction of Parliament of Canada to enact the Employment and Social Insurance Act* (1935, c. 48), 1936 CanLII 30 (SCC), [1936] SCR 427 at p.451.

²²⁶ Patented Medicine Prices Review Board, Alignment among public formularies in Canada, part 1 (2017), online: <<http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1327>>.

²²⁷ For instance, a 1991 study found that only seven of Canada’s (then) twelve provinces and territories covered such drugs under any circumstances. It notes that then-unmarketed HIV drugs like AZT “rocked” the system as part of a shift towards companies charging for unapproved drugs;

some procedure in place to pay, under certain circumstances, for a drug accessible only under the Special Access Programme.²²⁸ However, such provincial mechanisms can create their own complications. For instance, in one Ontario case, it was determined that the Ontario *Health Insurance Act* would cover out-of-country treatment with a cancer drug which was not marketed in Canada; another case confirmed this finding, but determined that the same Act would *not* cover the cost of the same drug acquired in Canada via the SAP.²²⁹ The Health Services Review and Appeal Board acknowledged this discrepancy, stating that the “unfortunate result arises from the legislation” and explaining that the Appeal Board “has reached this same conclusion in other cases: there is no mechanism to reimburse Mr. A. for that part of his treatment performed in Ontario even though it would have qualified as an insured treatment if performed out of the country”.²³⁰ Byzantine reimbursement mechanisms resulting in absurd outcomes such as this one are certainly something that should be addressed.

However, such provincial matters are ultimately secondary when it comes to access to medicines. As illustrated above, provinces play a vital role in the overall provision of Canadian healthcare, including pharmaceuticals. One thing they do *not* do, however, is exert control over which drugs are available in Canada in the first place.²³¹ The gatekeeping function of which drugs are available in Canada – regardless of who pays for them or where and how they are administered – is exercised by the federal government. This includes control over which drugs receive market approval under the *Food and Drugs Act*. It also includes the

the need for HIV and cancer drugs, and the shift to manufacturers charging for such drugs, in turn influenced provincial coverage. Clark, Edie & Canadian Coordinating Office for Health Technology Assessment, *A Survey of investigational new drug and emergency drug release policies* (Ottawa, Ont.: Canadian Coordinating Office for Health Technology Assessment, 1991).

²²⁸ See e.g., British Columbia, “6.2 Health Canada’s Special Access Programme Drugs” in *PharmaCare Policy Manual Version 1.0* (March 2012), online:

<<https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/pharmacare-publications/pharmacare-policy-manual-2012/understanding-pharmacare-benefit-status/health-canada-sap-drugs>>.

²²⁹ *Z.B. v. Ontario (Health Insurance Plan)*, 2009 CanLII 84997 (ON HSARB); *R.A. (Estate) v. Ontario (Health Insurance Plan)*, 2009 CanLII 85039 (ON HSARB).

²³⁰ *R.A. (Estate) v. Ontario (Health Insurance Plan)*, 2009 CanLII 85039 (ON HSARB).

²³¹ See e.g., Grignon, M et al., “The 2018 decision to establish an Advisory Council on adding pharmaceuticals to universal health coverage in Canada” (2020) 124:1 Health Policy 7–11.

channels by which unapproved drugs are accessed, such as the Special Access Programme, which is established under the *Food and Drug Regulations*. Thus, while provinces may sometimes play an important role in subsequent access to unmarketed medicines from a financial perspective, the actual presence or absence of the drug in the first place is distinctly federal.

Just as it brings to the fore other issues discussed in this thesis, the COVID-19 pandemic has firmly underscored the fact that provinces do not exert control over drug approval or access to unapproved drugs. This issue drew national attention in the wake of Alberta Premier Jason Kenney suggesting otherwise. In April 2020, he tweeted:

I have directed our officials to consider use of COVID19 tests, vaccines, or medications that have been approved by the high standards of at least one credible peer country's drug agency, e.g. @EMA_News [European Medicines Agency], @US_FDA [US Food and Drug Administration]. We won't wait for Health CDA to play catch up.²³²

He would assert this position again in the media.²³³ While the question of deferring to these foreign regulators will be revisited in this thesis, it will not be in a provincial context. In response to Kenney's remarks, expert legal commentators emphasized not only the long history of federal regulation in this space, such that any legal conflict between federal and provincial regimes would be resolved in favour of the former, but also the negative practical ramifications of a province (or ten provinces, of varying resources and abilities) suddenly embarking on an independent regulatory review.²³⁴ Federal primacy would be indirectly affirmed in

²³² Tweet cited in: French, Janet, "Alberta may circumvent Health Canada to gain access to COVID-19 tests and drugs, premier says", *CBC News* (13 April 2020).

²³³ Houston, Adam, "Jason Kenney and the pharmaceutical pipeline", *Rabble* (5 May 2020), online: <<https://rabble.ca/blogs/bloggers/views-expressed/2020/05/jason-kenney-and-pharmaceutical-pipeline>>.

²³⁴ Ogbogu, Ubaka & Lorian Hardcastle, "Crisis or not, Alberta must not do an end-run around Health Canada", *Globe and Mail* (20 April 2020), online: <<https://www.theglobeandmail.com/opinion/article-crisis-or-not-alberta-must-not-do-an-end-run-around-health-canada/>>.

practice in a subsequent attempt by another western Canadian premier to assert provincial control over access to COVID-19 vaccines: The otherwise self-aggrandizing announcement from Premier Brian Pallister that Manitoba had agreed to directly purchase two million doses of a novel mRNA COVID-19 vaccine from the Canadian company Providence Therapeutics acknowledges that Manitoba will receive its first doses “as soon as it is approved for sale in Canada”.²³⁵ As this illustrates, even amidst frictions between federal and provincial governments over access, it is the federal government that controls which medicines are available for purchase in the first place. As such, it is also the federal government which must take the necessary steps to improve access to off-patent Essential Medicines for Neglected Diseases.

Governing pharmaceuticals in Canada: The spending power, Essential Medicines and the Canada Health Act

For all the discussion of EMLs, formularies and pharmacopoeias contained within these pages, the most important list of drugs in Canada is almost certainly Health Canada’s Drug Product Database of medicines with marketing approval. While there is a long history of federal regulation in the pharmaceutical space, however, that federal role is less explicitly rooted in the constitutional division of powers. Indeed, only a few unquestionably health-focused areas are under federal jurisdiction, such as “Quarantine and the Establishment and Maintenance of Marine Hospitals”.²³⁶ Putting aside these particulars, federal authority in relation to health in general thus stems from a range of sources. These include, among others, Parliament’s authority to legislate in the area of criminal law, the federal government’s spending power, and, albeit in theory more than practice, its authority to ensure peace, order and good government (the POGG power).²³⁷ Of these powers, the criminal law power is the most important when it comes to

²³⁵ Government of Manitoba, “Manitoba Supports Made-in-Canada COVID-19 Vaccine to Protect Manitobans”, (11 February 2021), online: <https://news.gov.mb.ca/news/index.html?item=50742>.

²³⁶ Per s.91(11) *The Constitution Act, 1867*.

²³⁷ Jackman, Martha, “Constitutional Jurisdiction Over Health in Canada” (2000) 8 *Health Law Journal* 95–117.

pharmaceutical regulation and occupies the bulk of the following discussion. However, other powers, such as the spending power, also have an important role to play in relation to Essential Medicines.

The spending power is perhaps the constitutional power most obviously aligned with the Essential Medicines concept. Using it, the federal government can ultimately impact patient access to particular drugs. The spending power itself is a concept that crystallized well after Canadian Confederation and outside the explicit wording of the text; wider controversies over its applications are beyond the scope of this thesis.²³⁸ In brief, however, it provides the federal government with indirect influence over areas outside its explicit jurisdiction, by, in essence, providing funding with strings attached. Canada already uses the spending power to exercise influence over provinces in relation to drugs provided under the *Canada Health Act (CHA)*.²³⁹ In order to receive health transfer payments from the federal government, provinces must conform to criteria and conditions set out in the *CHA*. The Supreme Court of Canada has confirmed the constitutionality of influencing provincial activities around health in this way.²⁴⁰

In turn, the *CHA* creates its own category of drugs eligible for coverage. However, there are weaknesses to this categorization. It arises as part of the “hospital services” that *CHA* coverage is restricted to. Hospital services must be covered if “medically necessary for the purpose of maintaining health, preventing disease or diagnosing or treating an injury, illness or disability”; this includes “drugs, biologicals and related preparations when administered in the hospital”.²⁴¹ Medicines for patients outside this setting, no matter their medical importance, are not covered under the *CHA*, an artificial distinction divorced from the realities of healthcare. In response, it has been argued that physicians have the ability – and perhaps even a duty – to bridge this impractical divide between which drugs are covered and which are not by admitting patients to the hospital administratively, if

²³⁸ But if so inclined, see, as an interesting example, Telford, Hamish, “The Federal Spending Power in Canada: Nation-Building or Nation-Destroying?” (2003) 33:1 *Publius* 23–44.

²³⁹ *Canada Health Act*, R.S.C. 1985, c. C-6.

²⁴⁰ *Eldridge v. British Columbia (Attorney General)*, [1997] 3 S.C.R. 624 at para. 25.

²⁴¹ *Canada Health Act* (R.S.C., 1985, c. C-6) s.2.

not actually in practice, in order to ensure coverage for “essential medicines”.²⁴² This divide also fuels Canada’s patchwork of both public and private pharmaceutical coverage outside the *CHA*. This patchwork is complex; the 2019 federal budget suggested that more than 100 public programs and 100,000 private insurance plans were in place in Canada.²⁴³ This patchwork can in turn affect coverage for unmarketed Essential Medicines (provided they can be accessed in the first place).

The need for access to unmarketed Essential Medicines does not align with the artificial distinctions of the *CHA* either; the same underlying barriers to the formal availability of drugs can affect patients both inside and outside the hospital setting. At the same time, the *CHA* also raises another pertinent question regarding how drugs are classified in relation to their importance. Unfortunately, “medically necessary” is left undefined within the *CHA*, whether for drugs or for any other service. There is certainly no formulary or list of “medically necessary” drugs under the *CHA*. There are, however, obvious links to be made between Essential Medicines and “medically necessary” ones. Among those making these intuitive links are Canadian politicians and policymakers who have, whether intentionally or not, used these terms interchangeably, including in the context of recommending the federal government take action on compiling lists of important drugs.²⁴⁴ This connection can be drawn in other ways as well; Caulfield, for instance, draws the broader link between “medically necessary” in the *CHA* and the right to a basic level of healthcare found in numerous international instruments to which Canada is a party.²⁴⁵ As discussed in more detail elsewhere in this thesis, Essential Medicines

²⁴² As the quotation marks imply, this is an example where the term “essential medicines” is used but not formally defined. Wang, Annie, Trudo Lemmens & Navindra Persaud, “Medication access via hospital admission” (2017) 63:5 Can Fam Physician 344–347.

²⁴³ <https://www.budget.gc.ca/2019/docs/themes/pharmacare-assurance-medicaments-en.html>

²⁴⁴ See for instance the House of Commons Committee report, discussed in further detail later on, in which “essential”, “medically necessary” and “critical” are all used to describe important drugs, without definition or differentiation. Standing Committee on Health, Drug Supply in Canada: A Multi-Stakeholder Responsibility, 41st Parliament, 1st Session (2012), online: <<https://www.ourcommons.ca/Content/Committee/411/HESA/Reports/RP5640047/hesarp09/hesarp09-e.pdf>>.

²⁴⁵ Caulfield, Timothy A, “Wishful Thinking: Defining Medically Necessary in Canada” (1996) 4 Health LJ 63.

are today widely accepted as forming a core element of that right to a basic level of healthcare under international human rights law. Indeed, this latter point is today so widely accepted that at least one Canadian scholar has suggested the prevailing standard for a human right to health under international law is actually insufficient for HICs like Canada when it comes to pharmaceuticals, as if such a right “covers essential medicines, it is arguably of little value for the people of well-developed nations who are already entitled to those goods”.²⁴⁶ This statement reflects the unfortunate but not uncommon assumption that HICs have no need to take further action to ensure access to Essential Medicines at home, because their denizens already have access to them. Canadians with Neglected Diseases denied ready access to the global standard of care might disagree.

In any case, it is clear that the spending power can be used to influence access to important medicines, even if those medicines are ill-defined and, in the absence of universal pharmacare (revisited later), awkwardly restricted to a particular context. In turn, a clear definition, or defined point of reference, for “medically necessary” drugs would be useful for the *CHA* itself. A definition that was explicitly tied to Canadian treatment guidelines – a logical approach – would implicate numerous off-patent Essential Medicines for Neglected Diseases. It is also worth considering how others have used the term; while the US FDA’s formal definition of “medically necessary” is geared towards responding to the somewhat different issue of managing drug shortages, it explicitly states that “Off-label uses of approved drugs... and Investigational New Drug (IND) drugs may be considered medically necessary”, a definition that clearly encompasses drugs outside of formal approval for particular indications.²⁴⁷ As Donelle and colleagues have commented, drawing on this American approach to identifying “medically necessary” drugs in Canada “could also contribute to identifying products that belong on an eventual Essential Medicines list” as well as help identify broader concerns within the

²⁴⁶ Da Silva, Michael, “A Goal-Oriented Understanding of the Right to Health Care and its Implications for Future Health Rights Litigation” (2016) 39:2 Dal LJ 377.

²⁴⁷ Center for Drug Evaluation and Research, *Drug Shortage Management*, Manual of Policies and Procedures MAPP 4190.1 Rev. 3 (US FDA, 2018) at p.14-15.

pharmaceutical industry, including issues like supply chains for sole-source drugs, that will be revisited in later sections of this thesis.²⁴⁸

Provincial obligations under the *CHA* would be even clearer in the presence of an explicit EML or equivalent list of drugs. In the absence of a unified list or a clear definition of “medically essential”, different provinces have chosen to cover, or not cover, specific drugs in the context of the *CHA*.²⁴⁹ The consequence is that there have been gaps in pharmaceutical coverage that fall short of the five criteria that must be met in provincially administered public health care insurance plans under the *CHA*: public administration, comprehensiveness, universality, portability, and accessibility.²⁵⁰ Here too, however, even as scholars have recognized that provincial “discretion on how to define ‘medically necessary’ and ‘medically required’ can even allow some World Health Organization (WHO)-identified essential medicines to go uncovered throughout a province,” there has been little attention to the fact that some of these same Essential Medicines are not merely left without coverage by individual provincial plans, but are not formally available in Canada in the first place.²⁵¹ It is hard to argue an Essential Medicine recognized nationally and internationally as the standard of care isn’t medically necessary for a Canadian patient with that condition.

The issue of drug coverage under the *CHA* highlights a number of shortcomings of the existing approach to pharmaceutical access. It also illustrates how providing a clear reference point such as an explicit list of drugs would provide clarity around state obligations, and in turn patient entitlements. In doing so, it would also provide a means of standardizing the accessibility of important drugs across the country. While such a list could be applied strictly within the context of the *CHA*, it would also help to demonstrate that access to medicines in Canada is not an issue that can be artificially ended at the doors of the hospital; this

²⁴⁸ Donelle, Jessy, Jacalyn Duffin & Jon Pipitone. *Assessing Canada’s Drug Shortage Problem* (2018: CD Howe Institute).

²⁴⁹ Attaran, Amir, “Take your Medicine?: The Risk of Patient-led Litigation in Canada’s Medicine Access System” (2009) 3:1 *McGill Journal of Law and Health* 3–20.

²⁵⁰ S.7, *Canada Health Act* (R.S.C., 1985, c. C-6).

²⁵¹ Da Silva, Michael. Medicare and the Non-Insured Health Benefits and Interim Federal Health Programs: A Procedural Justice Analysis, (2017) 10:2 *McGill Journal of Law and Health* 101.

would in turn reinforce the need to take measures to ensure access to necessary drugs no matter where the patient receives them. This would itself underscore the importance of the federal government playing a role that goes beyond simply footing the bill to ensuring important drugs, be they medically necessary or Essential Medicines, are available in the first place.

Governing pharmaceuticals in Canada: The criminal law power & keeping drugs out

When it comes to the formal availability of drugs in Canada in the first place, federal regulation of pharmaceuticals is most heavily rooted in the criminal law power found under s.91(27). It has long been accepted that health is one of the “ordinary” ends of the criminal law.²⁵² In exercising this power, the federal government is able to address violations of its regulatory framework via fines and even imprisonment. As hinted earlier, the regulation of pharmaceuticals dates back almost to Confederation, with the first such law passed in 1874.²⁵³ In fact, with this law Canada became the first nation in the Americas to enact legislation regarding the adulteration of food and drugs on a national scale.²⁵⁴ As such, Canada’s initial foray into drug regulation actually predates America’s more famous *Pure Food and Drug Act* (1906) by over thirty years.²⁵⁵ Although ground-breaking in the Western Hemisphere, however, Canada’s instrument was not *sui generis*; this initial Canadian effort drew heavily from British legislation passed some years earlier.²⁵⁶ This story thus picks up where the earlier discussion of pharmacopeias left off;

²⁵² *Reference re Validity of Section 5 (a) Dairy Industry Act*, [1949] SCR 1, p.50, per Rand J.

²⁵³ *An Act To Impose License Duties on Compounders of Spirits, Amend the Act Respecting Inland Revenue, and To Prevent the Adulteration of Food, Drink and Drugs*. 1874 c. 8 S. C.

²⁵⁴ “Canada’s new food and drugs act” (1953) 44:11 Can J Public Health 424–425.

²⁵⁵ *Pure Food and Drug Act* (1906). United States Statutes at Large (59th Cong., Sess. I, Chp. 3915, p. 768–772; cited as 34 Stat. 768); Its fame may be partially tied to its links to Upton Sinclair’s landmark call to action *The Jungle* earlier that same year. Sinclair, Upton, *The Jungle* (New York: Grosset & Dunlap, 1906). In fairness, it should also be noted that the *Pure Food and Drug Act* was itself not quite the first such regulation in the United States; for instance, it was preceded by the *Biologics Control Act* of 1902, focusing on products like vaccines, serums and antitoxins. For an interesting history of the latter, see Coleman, Terry S, “Early Developments in the Regulation of Biologics” (2016) 71:4 Food Drug Law J 544–607.

²⁵⁶ Stieb, E W, “Drug adulteration: detection and control in Canada. A step forward: the Adulteration Act of 1884” (1976) 18:1 Pharm Hist 17–24.

Britain's first modern legislation regulating pharmaceuticals was enacted in 1860, and considerably expanded in 1872.²⁵⁷

This inaugural Canadian instrument of 1874 was the *Inland Revenue Act* (derived from the more cumbersome "Act To Impose License Duties on Compounders of Spirits, Amend the Act Respecting Inland Revenue, and To Prevent the Adulteration of Food, Drink and Drugs").²⁵⁸ Although the question of constitutionality was raised in the process of passing the *Inland Revenue Act*, notably in the Senate, the applicability of the federal criminal power ultimately won the day.²⁵⁹ Reception of the *Act* at the time was mixed. An editorial in the *Canadian Pharmaceutical Journal* remarked that it "bears abundant evidence of the haste which characterized its passage through Parliament, but still contains many good features, which, when perfected into a practicable and smoothly-working shape, will have a generally beneficial influence on the community".²⁶⁰ Such net-positive sentiments about regulation were not universally shared, however, including – not for the last time – by makers of pharmaceuticals.²⁶¹ As for its contents, the focus was on preventing Canadians from receiving adulterated products. The safety and efficacy of pharmaceuticals were yet to become priorities; however, Canadians could at least receive some assurances that they were receiving the product they'd paid for (whether or not that product actually did what it said on the tin). That said, while the *Act* defined the word "drug" to mean "all articles used for curative or medicinal purposes"; it oddly did not – in contrast to both food and drink – contain an explicit definition of what constituted an adulterated drug.²⁶²

²⁵⁷ Curran, RE, "British Food and Drug Law - A History" (1951) 6:4 Food, Drug, Cosmetic Law Journal 247–268. Around the same time, Britain had also consolidated the London, Edinburgh and Dublin pharmacopoeias into a single British Pharmacopoeia. Dunlop, D M & T C Denston, "The History and Development of the 'British Pharmacopoeia'" (1958) 2:5107 BMJ 1250–1252, online: <<https://www.bmj.com/lookup/doi/10.1136/bmj.2.5107.1250>>.

²⁵⁸ *An Act To Impose License Duties on Compounders of Spirits, Amend the Act Respecting Inland Revenue, and To Prevent the Adulteration of Food, Drink and Drugs*. 1874 c. 8 S. C.

²⁵⁹ See e.g., Debates and proceedings of the Senate of Canada : in the first session of the third Parliament of the Dominion of Canada. April 27, 1874. Pp.104-108. See also, Stieb, E W, "Drug adulteration: detection and control in Canada. A step forward: the Adulteration Act of 1884" (1976) 18:1 Pharm Hist 17–24.

²⁶⁰ "Editorial - The Adulteration Act" (1874) 7:12 The Canadian Pharmaceutical Journal 441–443.

²⁶¹ See e.g., "The Adulteration Act" (1874) 8:3 The Canadian Pharmaceutical Journal 97–98.

²⁶² *An Act To Impose License Duties on Compounders of Spirits, Amend the Act Respecting Inland*

The Canadian legislation was dramatically expanded in 1884, a move which took it out of the shadow of the measures in place in the UK.²⁶³ Once again, the question of jurisdiction was raised as the bill proceeded through Parliament and the application of the criminal power was again discussed; in the House of Commons it was observed that the party now objecting on such grounds was the very party that had passed the original *Inland Revenue Act* using the same constitutional justification.²⁶⁴ Notably, Canada's new *Adulteration Act* set standards against which to assess whether a drug had been adulterated.²⁶⁵ It also made the important distinction between harmful and benign adulteration.²⁶⁶ In an early example of Canada's longstanding tradition of recognizing foreign pharmaceutical standards, the reforms also included explicit acceptance of the British Pharmacopoeia and United States Pharmacopoeia as reference standards.²⁶⁷

Similar foreign reference standards would be adopted in the subsequent *Proprietary or Patent Medicine Act* of 1908, an unusual parallel regulatory system which required any drug *not* found in one of the recognized pharmacopoeias, or *not* providing its complete list of ingredients, to register its ingredients with the government.²⁶⁸ The *Adulteration Act* itself would be amended and consolidated in

Revenue, and To Prevent the Adulteration of Food, Drink and Drugs. 1874 c. 8 S. C.

²⁶³ Malleck, Dan, "Pure Drugs and Professional Druggists: Food and Drug Laws in Canada, 1870s-1908" (2006) 48:3 *Pharmacy in History* 103-115.

²⁶⁴ Stieb, EW, "Detection and Control in Canada: A Step Forward: The Adulteration Act of 1884" (1976) 18:1 *Pharmacy in History* 17-24.

²⁶⁵ *An Act To Amend and To Consolidate as Amended the Several Acts Respecting the Adulteration of Food and Drugs* 1884 C. 34 S. C.

²⁶⁶ Malleck, Dan, "Pure Drugs and Professional Druggists: Food and Drug Laws in Canada, 1870s-1908" (2006) 48:3 *Pharmacy in History* 103-115.

²⁶⁷ Art. 2(a)(1), *An Act To Amend and To Consolidate as Amended the Several Acts Respecting the Adulteration of Food and Drugs* 1884 C. 34 S. C.

²⁶⁸ For clarity, this legislation governed patent medicines (think proprietary products with names like Prof. Hinklebottom's Fantabulous Wonder Serum), not patented medicines. This was also the beginning of an odd bifurcation in Canadian drug regulation that would persist for decades, with drugs found in recognized pharmacopoeias regulated under other legislation such as the soon-to-be enacted *Food and Drugs Act*, and proprietary products under this one. While beyond the scope of this thesis, an interesting discussion of these parallel regimes can be found in Soucy, Paul, "The Proprietary or Patent Medicine Act of Canada" (1953) 8:11 *Food Drug Cosm LJ* 706. Nonetheless, the *Proprietary or Patent Medicine Act* placed some restrictions on ingredients to protect the safety of consumers, including the requirement that certain ingredients, like arsenic and morphine, be listed on the label. For an interesting early discussion of the Act, see "The Unsatisfactory Canadian Patent Medicine Act" (1909) LIII:13 *JAMA* 1034, online: <<http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.1909.02550130050008>>.

subsequent years, until it was replaced in 1920 with the *Food and Drugs Act*.²⁶⁹ The next iteration of the *Food and Drugs Act*, in 1927, would be the focus of a case that would affirm the importance of the criminal law power for regulation.²⁷⁰ Although the B.C. Court of Appeal's widely cited ruling in the 1933 *Standard Sausage* case referred – as the citation itself would imply – to adulteration of food, not drugs, under the *Food and Drugs Act*, the principles it highlights easily apply to the adulteration of pharmaceuticals as well. As the court stated:

[I]f the Federal Parliament, to protect the public health against actual or threatened danger, places restrictions on, and limits the number of preservatives that may be used, it may do so under s. 91 (27) of the B.N.A. Act. This is not in essence an interference with property and civil rights. That may follow as an incident but the real purpose (not colourable and not merely to aid what in substance is an encroachment) is to prevent actual, or threatened injury or the likelihood of injury of the most serious kind to all the inhabitants of the Dominion.²⁷¹

The ambit of pharmaceutical regulation would continue to expand in the ensuing decades, a story picked up again later. From the perspective of recognizing federal jurisdiction, however, the constitutionality of the *Food and Drugs Act* in the explicit context of pharmaceuticals rather than sausages was affirmed half a century after *Standard Sausage* by the Supreme Court of Canada in *Wetmore*, with Chief Justice Laskin, delivering the majority judgment, stating that “it has been well

²⁶⁹ *An Act Respecting Food and Drugs* 1920 c. 27 S. C. This was not the only federal legal reform in the realm of health in the aftermath of WWI; the Federal Department of Health had been created only the year before, in the wake of the Spanish Flu and the recognition of the need for national coordination on certain health issues. *An Act respecting the Department of Health*, (1919). Canada 8-9 George V, Parliament of the United Kingdom; 9-10 George V, 13th Parliament, 2nd Session, 1919(9-10 George V, 13th Parliament, 2nd Session), 87-90; see more broadly Humphries, Mark. *The Last Plague: Spanish Influenza and the Politics of Public Health in Canada* (University of Toronto Press, 2012).

²⁷⁰ *Food and Drugs Act*, R.S.C. 1927, c. 76.

²⁷¹ *Standard Sausage Co. v. Lee. Proctor v. Standard Sausage Co.*, 1933 CanLII 282 (BC CA) at p.506.

understood over many years that protection of food and other products against adulteration and to enforce standards of purity are properly assigned to the criminal law”.²⁷² The potential of the criminal law power in relation to health was expanded even wider some years later in *RJR-MacDonald v. Canada (Attorney General)*, with Justice LaForest stating that the “scope of the federal power to create criminal legislation with respect to health matters is broad, and is circumscribed only by the requirements that the legislation must contain a prohibition accompanied by a penal sanction and must be directed at a legitimate public health evil”.²⁷³

The key message here is that the criminal law power has long been central to the federal government’s efforts to keep Canadians safe via health regulation. Conceptions of what such protection entails in relation to pharmaceuticals have expanded since the initial concerns about adulteration, ultimately leading to the modern issues of safety, efficacy and quality. Crucially, however, while the criminal law power is used to protect Canadians from unsafe or ineffective drugs, that power is rooted in proscription of bad drugs, not prescriptions for good ones; it can protect Canadians from drugs they should not have, but cannot effectively protect them by ensuring they have access to those that they should. While Health Canada has numerous measures in place under the *Food and Drugs Act* and its regulations to evaluate a drug that someone wants to sell in Canada, as well as powers to ensure an unsafe drug is removed from the market, it has virtually no powers in place to make sure an Essential Medicine remains available in Canada, or indeed is brought to market here in the first place. If a manufacturer decides, for commercial reasons, not to enter the Canadian market, or to stop selling a drug in Canada, there is very little Canada can do to intervene, regardless of the impact on the health of patients.

To drive this point home, imagine that Health Canada is a bit like the bouncer working the door at a nightclub. For a drug to enter Club Canada, the bouncer scrutinizes the documents it provides (with scientific studies taking the

²⁷² *R. v. Wetmore*, [1983] 2 S.C.R. 284 at p.288-289.

²⁷³ *RJR-MacDonald v. Canada (Attorney General)*, [1995] 3 S.C.R. 199, para. 32.

place of personal ID). Only if the drug and its documents pass muster – and if it pays the cover charge, in the form of regulatory fees – will it be allowed past the velvet rope into the Canadian health system. In turn, the bouncer also assumes a security role within the club; if a drug turns out to be a safety hazard once inside, Health Canada can boot it back out, removing it from the market. However, this model is dependent upon the premise that Club Canada is a desirable destination in the first place. If there are drugs that would enliven the scene, but have no interest in entering, the bouncer has exceedingly limited means by which to entice them to come in; it might waive the cover charge, or let them jump the queue. Similarly, if a drug wants to leave – it decides the scene at Club Canada is no longer appealing – there’s no way to prevent it from departing of its own volition. Strained analogies aside, this is the fundamental problem when it comes to many off-patent Essential Medicines for Neglected Diseases. While safety, quality and efficacy are the cornerstones of pharmaceutical regulation, a dogmatic approach to these elements, particularly making them subservient to commercial interest, can actually exacerbate access barriers, ultimately having a negative impact on the health of patients without ever actually realizing any of these regulatory goals.²⁷⁴

Governing pharmaceuticals in Canada: Other federal powers

There are other federal powers with implications for pharmaceuticals that should be acknowledged as well, even if they do not play so central a role in the current story. For instance, the Supreme Court of Canada has left open the question whether, in addition to the criminal law power, the trade and commerce power might also be implicated by the *Food and Drugs Act*.²⁷⁵ Canada’s complex relationship with access to medicines is also reflected within Canada’s even more complex historical relations with Indigenous communities; COVID-19 has also

²⁷⁴ This balance of safety, efficacy and quality concerns not always aligning with pricing and supply concerns is not unique to Canada, but is a concern in other countries as well. See e.g., Messing, Edward M, “The BCG Shortage” (2017) 3:3 BLC 227–228, online: <<https://www.medra.org/servlet/aliasResolver?alias=iospress&doi=10.3233/BLC-179018>>.

²⁷⁵ *R. v. Wetmore*, [1983] 2 S.C.R. 284 at p.288. This issue has been flagged before, including in the concurring judgment of Martin, J.A. in the addendum, *Standard Sausage Company v. Lee*, 1934 CanLII 344 (BC CA) at p.112.

served to highlight this intersection.²⁷⁶ There is also another clearly established source of federal power when it comes to the regulation of pharmaceuticals in particular: Federal jurisdiction over “Patents of Invention and Discovery”.²⁷⁷ Although, as noted, this thesis intentionally sidelines patents, they are nonetheless an important element of broader pharmaceutical governance in Canada. An unfortunate consequence of this is that federal governance of pharmaceuticals rooted in the patent power serves to de-emphasize off-patent drugs. For instance, the Patented Medicine Prices Review Board (PMPRB), Canada’s key tool for tackling excessive drug prices, is established under the *Patent Act*.²⁷⁸ As such, it has no jurisdiction to address issues such as the high prices for off-patent drugs accessed through the SAP like cycloserine. More broadly, as shall be seen, the distinction between on-patent and off-patent drugs (and the imperfect relationship between patent status and whether a drug is “old” or “new” in the context of Canadian pharmaceutical regulation) may also not always align with other regulatory goals.

Lastly, when it comes to federal jurisdiction, it should also be recognized that in some instances the federal government itself provides services similar to those normally associated with the provinces. In particular, it already provides

²⁷⁶ This fascinating area is beyond the scope of this thesis. However, as a key example, Treaty 6, covering much of what is today central Alberta and Saskatchewan, is the only treaty between the Crown and First Nations to include both a provision providing for relief in case of pestilence or famine, and one stating “[t]hat a medicine chest shall be kept at the house of each Indian Agent for the use and benefit of the Indians at the direction of such agent”. Crown-Indigenous Relations and Northern Affairs Canada, *Treaty No. 6* (Ottawa: Queen’s Printer and Controller of Stationary, 1964), online: Treaty Texts <<https://www.rcaanc-cirnac.gc.ca/eng/1100100028710/1581292569426>>. The precise extent of these treaty rights in relation to healthcare in general has long been a matter of debate, but an expansive interpretation in relation to access to medicines has been consistently clear. See e.g., *R. v. Johnston*, 1966 CanLII 341 (SK CA); *Northern Inter-Tribal Health Authority Inc. v. Canada (Attorney General)*, 2018 FC 1180 (CanLII), [2019] 2 FCR 714. Although Treaty 6 is the only treaty with an explicit clause to this effect, it has been used, in conjunction with oral histories of treaty negotiations, to incorporate similar rights into other numbered treaties. *Northern Inter-Tribal Health Authority Inc. v. Canada (Attorney General)*, 2018 FC 1180 (CanLII), [2019] 2 FCR 714. Furthermore, this clause still resonates; early in the COVID-19 pandemic, the four First Nations of Maskwacis issued a declaration intended to activate the medicine chest and famine & pestilence clauses of Treaty 6. Dubois, Stephanie, “Maskwacis activates ‘medicine chest’ treaty clause, declaring state of emergency”, *CBC News* (24 March 2020), online: <<https://www.cbc.ca/news/canada/edmonton/maskwacis-state-of-emergency-medicine-chest-treaty-clause-covid-19-coronavirus-1.5507902>>.

²⁷⁷ Per s.91(22).

²⁷⁸ S.91(1), *Patent Act* (R.S.C., 1985, c. P-4).

pharmaceutical coverage to a range of specific classes of people, including federal inmates, members of the armed forces, and “aliens” falling within the scope of its s.91 jurisdiction. In practice, this has meant direct federal acknowledgment of the importance of accessing unapproved drugs, including off-patent Essential Medicines for Neglected Diseases, for the health of people under its care. As a prime example, the Interim Federal Health Program (IFHP) provides temporary, limited health-care benefits to resettled refugees, refugee claimants, and similar groups who aren’t eligible for provincial or territorial funding. One component of the IFHP is supplementary drug coverage. According to the formulary of IFHP Additional Drug Benefits, claimants receive coverage for a number of medicines for Neglected Diseases, some of which are not covered by all provincial formularies, and others that do not currently have market approval in Canada.²⁷⁹ This latter category includes Neglected Disease drugs that are found on the WHO MEML (pyrimethamine, chloroquine), and others that are not (the amoebiasis drug diiodohydroxyquin and the anti-helminthic thiabendazole).²⁸⁰ In certain provinces (Saskatchewan, Alberta, Ontario, British Columbia and New Brunswick) it also covers TB drugs provided by the provincial TB program, which may include unmarketed Essential Medicines for TB.²⁸¹ There is some slight irony here given that when the Canadian government tried to justify its controversial 2012 cuts to the IFHP in the courtroom, part of their argument was that the IFHP provided better care to non-Canadians than Canadians, making the reforms a matter of “fairness for Canadians”; the Federal Court rejected this argument on the grounds it had not been established there was in fact anything unfair to Canadians about the IFHP before it was reformed, or that it was fairer after these reforms.²⁸² Despite the

²⁷⁹ Medavie Blue Cross, IFHP Benefit Grid – Prescription Drug (accessed 6 April 2022), online: <https://docs.medaviebc.ca/providers/benefit_grids/ifhp_benefit_grid_prescription_drug_coverage.pdf?mtime=20181205115932>.

²⁸⁰ Medavie Blue Cross, IFHP Benefit Grid – Prescription Drug (accessed 6 April 2022), online: <https://docs.medaviebc.ca/providers/benefit_grids/ifhp_benefit_grid_prescription_drug_coverage.pdf?mtime=20181205115932>.

²⁸¹ Medavie Blue Cross, IFHP Benefit Grid – Prescription Drug (accessed 6 April 2022), online: <https://docs.medaviebc.ca/providers/benefit_grids/ifhp_benefit_grid_prescription_drug_coverage.pdf?mtime=20181205115932> at Note 7.

²⁸² *Canadian Doctors for Refugee Care v. Canada (Attorney General)*, 2014 FC 651 at para. 952.

outcome of this case, it appears that in the very limited instance of certain unapproved drugs for Neglected Diseases, drug coverage for this non-citizen group under the IFHP may in fact be better than for the average Canadian. What this scenario really shows, however, is the importance of recognizing that vulnerable populations often have particular health needs that need to be met, which are not always effectively met by Canada's current pharmaceutical regulatory system, even where the drugs necessary to meet those needs are readily available elsewhere.

A provincial wrinkle – compounding

Before leaving the topic of constitutional jurisdiction entirely, however, there remain two issues within provincial jurisdiction that deserve further attention given their impacts on access to off-patent Essential Medicines for Neglected Diseases. In turn, they also serve to further illustrate the necessity of action at the federal level. Both involve provincial jurisdiction over health professions. One provides a partial, but insufficient, alternative to federal reforms to improve access; the other underscores the importance not merely of improved access, but of access to a formally marketed product.

The first of these is pharmaceutical compounding, which implicates pharmacists. The regulation of pharmacists has been specifically upheld as a matter of provincial jurisdiction.²⁸³ Canadian courts have referred to compounding as “a term which describes the practice of a licensed pharmacist when combining an active pharmaceutical ingredient with non-medicinal ingredients to create a customized drug in dosage form to meet a specific patient need as evidenced by a prescription from a physician”.²⁸⁴ However, there remain some tensions around the precise boundaries between compounding of pharmaceuticals (under provincial jurisdiction) and manufacturing them (which is federal).²⁸⁵ Health Canada has issued guidance stating that compounding “must be a legitimate part of the practice of regulated healthcare professionals and must not be used as a means to bypass

²⁸³ Notably in *Re Levkoe and The Queen*, 1977 CanLII 1088 (ON SC).

²⁸⁴ This definition was accepted by both parties in *Canadian Pharmaceutical Technologies International (C.P.T.) Inc. v. Canada (Attorney General)*, 2006 FC 708 (CanLII) at para. 2.

²⁸⁵ See e.g., Health Canada, *Health Products and Food Branch Inspectorate - Policy on Manufacturing and Compounding Drug Products in Canada*, POL-0051 (2009).

the federal drug review and approval system”.²⁸⁶ Similarly, it states that compounding a drug identical to a commercially available product will be considered manufacturing rather than compounding.²⁸⁷ What compounding *can* be used to do is to create a customized drug for an individual patient on demand. In addition to a completely unmarketed drug, compounding is often used to create a formulation of a marketed drug that is unavailable, such as a paediatric formulation; compounding may also be possible during a period of shortage of an otherwise marketed drug, although the precise legal boundaries for doing so remain largely untested.²⁸⁸

Compounding can serve as a useful stopgap measure for access to unmarketed off-patent Essential Medicines at the individual level. Some of the drugs discussed in this thesis are relatively easy to compound, given access to the right ingredients; for instance, a group of Australian high school students attracted media attention for producing pyrimethamine in response to the American price hike by the infamous Martin Shkreli.²⁸⁹ Similarly, before ivermectin finally reached the Canadian market, some physicians were able to successfully use compounding pharmacies for access in some instances.²⁹⁰ However, compounding depends on a range of factors, including the availability of the active pharmaceutical ingredient (API). In Canada, these ingredients have been more tightly regulated since 2013, when the *Food and Drug Regulations* were amended to include them.²⁹¹ It also

²⁸⁶ See e.g., Health Canada, *Health Products and Food Branch Inspectorate - Policy on Manufacturing and Compounding Drug Products in Canada*, POL-0051 (2009).

²⁸⁷ See e.g., Health Canada, *Health Products and Food Branch Inspectorate - Policy on Manufacturing and Compounding Drug Products in Canada*, POL-0051 (2009).

²⁸⁸ Health Canada, *Health Products and Food Branch Inspectorate - Policy on Manufacturing and Compounding Drug Products in Canada*, POL-0051 (2009).

²⁸⁹ Hunjan, Raveen, “Daraprim drug’s key ingredient recreated by high school students in Sydney for just \$20”, *ABC News Australia* (30 November 2016), online: <<https://www.abc.net.au/news/2016-11-30/daraprim-nsw-students-create-drug-martin-shkreli-sold/8078892>>.

²⁹⁰ Houston, Adam R et al., “Reforming Canada’s Special Access Programme (SAP) to improve access to off-patent essential medicines” (2018) 3:2 *Official Journal of the Association of Medical Microbiology and Infectious Disease Canada* 100–107, online: <<http://jammi.utpjournals.press/doi/10.3138/jammi.2018.01.04>>.

²⁹¹ “Regulations Amending the Food and Drug Regulations (1475 — Good Manufacturing Practices)”, *Canada Gazette* (8 May 2013) Vol. 147, No. 10, online: <https://gazette.gc.ca/rp-pr/p2/2013/2013-05-08/html/sor-dors74-eng.html>; Health Canada, “Active Pharmaceutical Ingredients - Good Manufacturing Practices - Questions and Answers” (21 January 2014), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance->

depends on the availability of compounding pharmacies and pharmacists; for instance, while large hospitals in major Canadian cities may be capable of producing pediatric formulations of tuberculosis medicines, small communities in Nunavut, bearing the brunt of the disease, often do not have the same capacity.²⁹² Furthermore, the use of compounding raises questions of safety, efficacy and quality that may be harder to regulate and assess on a consistent basis. The United States offers a recent cautionary tale of how compounding can go wrong: in 2012 and 2013, at least 60 people died as a result of fungal meningitis contracted through contaminated injectable drugs compounded at a single facility.²⁹³ In that instance, a similar jurisdictional split between states and the federal government ultimately led to lax regulation of compounding; while legal reforms were enacted to improve standards in the wake of this disaster, it is a reminder of the potential risks of this approach to supplying drugs, particularly where enforcement is subpar.²⁹⁴ In Canada, because compounding is under provincial jurisdiction, there are similarly no uniform national legal standards. Those national standards that do exist are voluntary, such as those promulgated by the (Canadian) National Association of Pharmacy Regulatory Authorities in the wake of the American disaster.²⁹⁵

enforcement/information-health-product/drugs/active-pharmaceutical-ingredients-questions-answers.html>.

²⁹² Nash, Madlen & Rachel Kiddell-Monroe, “Making the case for child-friendly TB treatment for Inuit: challenging Canada’s double standard”, (6 November 2018), online: *Nature Portfolio Microbiology Community* <<https://naturemicrobiologycommunity.nature.com/posts/40701-making-the-case-for-child-friendly-tb-treatment-for-inuit-challenging-canada-s-double-standard>>.

²⁹³ Centers for Disease Control and Prevention. “Multi-state meningitis outbreak—current case count. 2013 [Note: Cases no longer added after October 2015]”, online: <<http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html>>. There have been suggestions that this number is an underestimate. See e.g., Roche Jr, Walter F, “Number deaths caused by the 2012 fungal meningitis outbreak underreported”, *The Nashville Tennessean* (31 December 2018), online: <<https://www.tennessean.com/story/news/health/2018/12/31/number-deaths-caused-2012-fungal-meningitis-outbreak-underreported/2447091002/>>.

²⁹⁴ Teshome, Besu F et al., “How gaps in regulation of compounding pharmacy set the stage for a multistate fungal meningitis outbreak” (2014) 54:4 *J Am Pharm Assoc* (2003) 441–445.

²⁹⁵ Rose, Alex, “Canada is tightening its drug compounding regulations”, *The Signal* (24 March 2017), online: <<https://signalhfx.ca/canada-is-tightening-its-drug-compounding-regulations/>>; National Association of Pharmacy Regulatory Authorities, “NAPRA Compounding Standards Implementation” (5 May 2021), online: <<https://napra.ca/news-notice/napra-compounding-standards-implementation>>.

Ultimately, the existence of compounding, and its utility in some situations, should not be ignored. However, compounding is, by design, intended to operate reactively, at the level of the individual patient; it is clearly not a systemic solution. Reliance on compounding can also introduce further uncertainty. For instance, in a recent instance where a child in Lethbridge required prompt access to albendazole after consuming raccoon feces infested with the parasite *Baylisascaris procyonis*, it required an effort spanning a multiple provinces to track down a compounding pharmacy with both the ingredients and ability to make the drug.²⁹⁶ This scenario of children requiring albendazole after ingesting raccoon feces is actually sufficiently common in Canada that it is the subject of specific guidelines in the medical literature.²⁹⁷ Affected children should have dependable access to treatment. This underscores why, rather than relying on compounding, a systemic solution to ensuring Essential Medicines are readily accessible in Canada is necessary.

Another provincial wrinkle – off-label prescribing

The second issue stemming from provincial jurisdiction over healthcare professionals underscores further barriers arising from the regulatory disjunct between medicines formally available in Canada and those which are not. The barriers to accessing Essential Medicines that are not approved by Health Canada, even where they are part of both international and domestic treatment guidelines, are highlighted throughout this thesis. However, once a drug is formally approved in Canada, physicians have considerably more autonomy over how to use that drug, regardless of its formal indications. Health Canada approval includes several stipulations, including the indication (or indications) the drug can be used for, the dosage that can be administered, and the population(s) to whom the drug can be prescribed. After a drug is approved, however, Health Canada has less control over

²⁹⁶ Kost, Hannah, “With clock ticking, doctors, pharmacists come to the rescue after 1-year-old eats raccoon feces”, *CBC News* (19 June 2021), online:

<<https://www.cbc.ca/news/canada/calgary/alberta-infant-eats-raccoon-feces-1.6069633>>.

²⁹⁷ Kazmi, Kescha, Fatimah Al Dubisi & Shaun K Morris, “Raccoon roundworm infection: What a child health care practitioner in Canada needs to know about a rare but important zoonotic helminth infection” (2019) 24:3 *Paediatrics & Child Health* 135–136, online:

<<https://academic.oup.com/pch/article/24/3/135/5274187>>.

how licenced healthcare providers use it in practice.²⁹⁸ The consequence is that physicians (and other provincially regulated healthcare practitioners with the ability to prescribe) have wide discretion over off-label prescribing – that is, prescribing Health Canada-approved drugs for conditions or populations outside of that approval. Broadly speaking, off-label prescribing has been recognized by Canadian courts not only as a legal practice by physicians, but a common one.²⁹⁹ While Canadian statistics are sparse, one study in Quebec found 11% of prescriptions were off-label.³⁰⁰ For some conditions and populations, it can be considerably higher. The practice is commonplace not only in Canada, but many other jurisdictions.³⁰¹ Off-label use has occasionally drawn political attention in Canada, including from the Senate in 2014, but the underlying ability of physicians to prescribe off-label has not come into serious question.³⁰²

This freedom is subject to certain limitations, such as ensuring informed consent, and meeting the duty of care.³⁰³ Canadian courts have found that

²⁹⁸ Interestingly, there has been a recent shift toward recognizing the realities of off-label use in another area that does remain largely under federal control: clinical trials research. In 2019, Health Canada acknowledged that its requirement that a drug marketed in Canada be treated as an investigational drug if being used off-label in a clinical trial “may be creating an unnecessary barrier to clinical research” as “the off-label uses of an authorized drug can often be supported by well-established clinical practice overseen by provincial bodies that govern medical practice”. Health Canada, “Notice to Stakeholders: Statement on the Investigational Use of Marketed Drugs in Clinical Trials”, (31 October 2019), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/notice-statement-investigational-use-marketed-drugs-clinical-trials.html>>.

²⁹⁹ See e.g., *Goodridge v. Pfizer Canada Inc.*, 2010 ONSC 1095 at para.14.

³⁰⁰ Egale, Tewodros et al., “Association of Off-label Drug Use and Adverse Drug Events in an Adult Population” (2016) 176:1 JAMA Intern Med 55, online: <<http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2015.6058>>.

³⁰¹ For a particularly thorough legal analysis of the legal aspects of off-label use in the United States, see Beck, James M., “Off-Label Use in the Twenty-First Century: Most Myths and Misconceptions Mitigated” 54:1 (John Marshall Law Review) 1–122. As another international example, see Doms, Marc, David Cassiman & Steven Simoons, “Off-label use of orphan medicinal products: a Belgian qualitative study” (2016) 11:1 Orphanet J Rare Dis 144, online: <<http://ojrd.biomedcentral.com/articles/10.1186/s13023-016-0507-y>>; Gupta, Sandeep Kumar & Roopa Prasad Nayak, “Off-label use of medicine: Perspective of physicians, patients, pharmaceutical companies and regulatory authorities” (2014) 5:2 J Pharmacol Pharmacother 88–92; Stafford, Randall S., “Regulating Off-Label Drug Use — Rethinking the Role of the FDA” (2008) 358:14 N Engl J Med 1427–1429, online: <<http://www.nejm.org/doi/abs/10.1056/NEJMp0802107>>.

³⁰² Standing Senate Committee on Social Affairs, Science and technology, *Prescription Pharmaceuticals in Canada - Off-Label Use*, (Ottawa, 2014), online: <<https://sencanada.ca/content/sen/Committee/412/soci/rep/rep05jan14-e.pdf>>.

³⁰³ Paulsen, Natalie de, “The Regulatory Gap: Off-Label Drug Use in Canada” (2005) 63 University of Toronto Law Review 183–211.

“prescribing practices that run contrary to express warnings against such use from the manufacturer” fall outside the boundaries of permissible off-label prescribing.³⁰⁴ Similarly, COVID-19 has drawn particular attention to the off-label prescribing of drugs such as ivermectin, despite lack of evidence for that indication; against this backdrop, professional bodies have imposed sanctions on individual physicians, such as practice restrictions prohibiting them from prescribing certain drugs off-label for COVID-19.³⁰⁵ Ultimately, however, the physician likely has considerable leeway; as the Supreme Court of Canada has said, “Given the number of available methods of treatment from which medical professionals must at times choose, and the distinction between error and fault, a doctor will not be found liable if the diagnosis and treatment given to a patient correspond to those recognized by medical science at the time, even in the face of competing theories”.³⁰⁶ In Canada, analysis of liability for off-label use has traditionally focused upon the degree of evidence to support that off-label use.³⁰⁷ While off-label prescribing can have risks, these risks are mitigated where it is done with the support of scientific evidence.³⁰⁸

Off-label use may occur for a range of reasons, including use for similar conditions (for instance, a drug approved for a particular cancer being used for another similar cancer), or because no approved treatment is available for a particular population. Children, for instance, are often excluded from the scope of drug approvals, meaning use of many drugs in paediatric populations is off-label.³⁰⁹ Recognition of the special needs of children is one reason that the WHO has published a specific Model List of Essential Medicines for children (MEMLc)

³⁰⁴ *Fowlow v. Gupta*, 2012 ONSC 6531 at para. 77.

³⁰⁵ See e.g., Loriggio, Paola, “Restrictions imposed on doctor accused of spreading COVID misinformation”, *CP 24* (28 September 2021), online: <<https://www.cp24.com/news/restrictions-imposed-on-doctor-accused-of-spreading-covid-misinformation-1.5603511>>.

³⁰⁶ *Lapointe v. Hôpital Le Gardeur*, [1992] 1 S.C.R. 351

³⁰⁷ Paulsen, Natalie de, “The Regulatory Gap: Off-Label Drug Use in Canada” (2005) 63 *University of Toronto Law Review* 183–211.

³⁰⁸ Egualé, Tewodros et al., “Association of Off-label Drug Use and Adverse Drug Events in an Adult Population” (2016) 176:1 *JAMA Intern Med* 55, online: <<http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2015.6058>>.

³⁰⁹ See e.g., “Prescribing off-label drugs for children: when will it change?” (2019) 394:10204 *The Lancet* 1114, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673619322123>>.

alongside the WHO MEML since 2007.³¹⁰ In turn, narrow approval means many Essential Medicines, including for Neglected Diseases, may not be approved for children in all jurisdictions where they are approved for adults, leaving them to be used off-label.³¹¹

Other times, as in the case of the early months of the COVID-19 pandemic, off-label prescribing may occur because no treatments are approved for that condition at all.³¹² This is also a reason it is widely used for Rare Diseases, something noted by the Canadian Senate in their examination of off-label prescribing.³¹³ Off-label use can occur with new drugs; indeed, in the United States, some drugs that have benefited from particular initiatives intended to promote access to drugs serving small populations, such as Orphan Drug legislation, have in practice ended up being far more widely used off-label for more common conditions, highlighting the potential to exploit such initiatives.³¹⁴ However, off-label prescribing often occurs with older drugs.³¹⁵ This is in part because the longer a drug is in use, the more opportunity there is for physicians to become familiar with it and to use it (or for researchers to study it) in a novel way. In turn, these off-label uses often stay off-label; while it is generally possible for a pharmaceutical company to apply to a regulator to expand the formal approval for a drug, be it for

³¹⁰ WHO Expert Committee on the Selection and Use of Essential Medicines (2007 : Geneva, Switzerland) & World Health Organization. (2007). WHO model list of essential medicines for children : 1st list, October 2007.

³¹¹ For instance, a 2017 review conducted of the approval of the 349 medicines included on the 5th MEMLc in Japan, the United States and the UK found that of the 39 MEMLc-listed medicines that were not approved in any of the three countries for pediatric indications, 26 were for Neglected Diseases. Shimazawa, Rumiko & Masayuki Ikeda, "Approval status and evidence for WHO essential medicines for children in the United States, United Kingdom, and Japan: a cross-sectional study" (2017) 10 J Pharm Policy Pract 4.

³¹² Kalil, Andre C, "Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics" (2020) 323:19 JAMA 1897, online: <<https://jamanetwork.com/journals/jama/fullarticle/2763802>>.

³¹³ Standing Senate Committee on Social Affairs, Science and technology, *Prescription Pharmaceuticals in Canada - Off-Label Use*, (Ottawa, 2014), online: <<https://sencanada.ca/content/sen/Committee/412/soci/rep/rep05jan14-e.pdf>>.

³¹⁴ Orphan drug legislation will be explored in more depth later. Kesselheim, Aaron S et al., "The Prevalence and Cost of Unapproved Uses of Top-Selling Orphan Drugs" (2012) 7:2 PLoS ONE e31894, online: <<https://dx.plos.org/10.1371/journal.pone.0031894>>.

³¹⁵ Egualé, Tewodros et al., "Association of Off-label Drug Use and Adverse Drug Events in an Adult Population" (2016) 176:1 JAMA Intern Med 55, online: <<http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2015.6058>>.

new indications or populations, the company may not wish to go to the time and expense of doing so, particularly for an off-patent drug and a use serving a small population.³¹⁶ In some instances, filing for a new indication (in Canada, via a Supplemental New Drug Submission, SNDS) might even be a commercial risk for the manufacturer, if a product already widely used off-label turns out to be unsafe or ineffective for that indication.³¹⁷ Instead, knowledge of off-label uses may spread in the academic literature and via word of mouth among health professionals. This itself raises some interesting legal questions. In Canada, advertising an off-label use for a drug is prohibited under the *Food and Drugs Act*.³¹⁸ This prohibition is also recognized in the Code of the Pharmaceutical Advertising Advisory Board (PAAB), an independent not-for-profit agency that reviews advertising for healthcare products, which notes that an “advertisement is misleading if it suggests that a drug is useful in a broader range of conditions or patients than that which have been approved by Health Canada”.³¹⁹ At the same time, a drug may nonetheless be widely used off-label, even becoming the standard of care. In fact, while sometimes off-label prescribing may be indirectly restricted by provincial (or private) insurance that only covers approved indications for a given drug rather than unrestricted use of that drug, at other times provinces may actively encourage off-label use.³²⁰

³¹⁶ See e.g., Horton, John. “Echinococcosis and Albendazole: A Case for Suitable Treatment” (2018) 99:4 *The American Journal of Tropical Medicine and Hygiene* 811–812, online: <<http://www.ajtmh.org/content/journals/10.4269/ajtmh.18-0609>>.

³¹⁷ Paulsen, Natalie de, “The Regulatory Gap: Off-Label Drug Use in Canada” (2005) 63 *University of Toronto Law Review* 183–211.

³¹⁸ Rooted in s.9(1). While outside the scope of this section, it is worth noting that promotion of off-label use is one area where Canada and the US have followed very different paths. In the latter country, promotion of off-label use has been a lightning rod for free speech concerns. These manifested most notably in *United States v. Caronia*, No. 09-5006 (2d Cir. 2012), which found that truthful promotion of off-label use was protected under the First Amendment of the U.S. Constitution. See also, Greene, Stephanie M & Lars Noah, “Off-Label Drug Promotion and the First Amendment” (2014) 162 *University of Pennsylvania Law Review*, online: <https://scholarship.law.upenn.edu/penn_law_review_online/vol162/iss1/6>; Liu, Sheng, Michelle M Mello & Aaron S Kesselheim, “Prospects for Enforcing Prohibitions on Off-Label Drug Promotion after *United States v. Caronia*: An Analysis of Litigated Cases” (2021) 46:3 *J Health Polit Policy Law* 487–504.

³¹⁹ Pharmaceutical Advertising Advisory Board, *The PAAB Code of Advertising Acceptance* (2018), online: <https://code.paab.ca/pdfs/paab_code_Word_Official%20.pdf> at s.2.10.

³²⁰ To give one prominent example from outside the realm of Neglected Diseases, the B.C. Provincial Retinal Diseases Treatment Program, under which the Province of British Columbia provides free

What does off-label prescribing have to do with off-patent Essential Medicines for Neglected Diseases? Quite a bit. For example, even though an anti-parasitic drug like ivermectin or albendazole may be the best treatment for a range of parasitic Neglected Diseases, it may not have formal approval as a treatment for all of those indications anywhere, let alone in one specific country. This is unsurprising, particularly as new uses are discovered; if a drug is already commercially unappealing, going to the time and expense of adding further indications for such a drug once it is on the market is likely to be even less so. However, formal approval for at least one indication opens the door to off-label use; this means that although ivermectin is only approved for treating intestinal strongyloidiasis and onchocerciasis in Canada – just one quarter of the indications found on the WHO MEML – practitioners can (and do) now use it for other Neglected Diseases. Indeed, now that ivermectin is approved in Canada, its use for other Neglected Diseases has drawn increased attention, including a Canadian

treatment for certain diseases of the eye, relies heavily on the use of bevacizumab, approved in Canada for the treatment of certain cancers, for the off-label treatment of macular degeneration. Grant, Kelly, “B.C. eye-injection program ‘clouded in secrecy’”, *Globe and Mail* (27 January 2020), online: <<https://www.theglobeandmail.com/canada/article-bc-eye-injection-program-clouded-in-secrecy/>>. One of the main reasons the provincial government prioritizes bevacizumab, which it uses in 85% of cases under the program, is because it is considerably cheaper than its closest comparator, ranibizumab, although only the latter is actually approved in Canada for macular degeneration. Thus, a provincial government actively finances an off-label use over an alternative drug approved by Health Canada for that indication, which is only used in 1% of cases. Government of British Columbia, “Keeping eye treatments safe, accessible and available for British Columbians”, (24 May 2019), online: <<https://news.gov.bc.ca/releases/2019HLTH0078-001060>>. The bevacizumab story isn’t unique to Canada, however; it is also on the WHO MEML for the same condition of macular degeneration. The inclusion of off-label usages on the WHO MEML has been questioned. Gray, Andy L et al. “Essential medicines are still essential” (2015) 386:10004 *The Lancet* 1601–1603. Nevertheless, while the WHO Expert Committee has acknowledged the absence of Stringent Regulatory Authority approval for this indication, it nonetheless recommended it be added to the MEML on the grounds of public health need, demonstrated safety and effectiveness, and favourable cost–effectiveness. WHO Expert Committee on the Selection and Use of Essential Medicines ed, *The selection and use of essential medicines: report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children)*, WHO technical report series 985 (Geneva, Switzerland: World Health Organization, 2014) at p.72. Furthermore, as B.C.’s retinal disease program suggests, off-label use can also serve the prioritization of sustainably priced public health programming over commercial interests. All of this said, however, it remains difficult to use a drug off-label if that drug is not approved in the first place.

Agency for Drugs and Technologies in Health (CADTH) review of its use for scabies that explicitly acknowledges the use in question is off label.³²¹

Narrow formal approval can still have consequences, however. Sometimes, these can be relatively minor frustrations; for instance, in jurisdictions where albendazole is licensed only for particular indications, concerns have been raised about the fact that the drug is packaged and sold with those indications in mind, rather than in the forms or amounts best suited to other Neglected Diseases like echinococcosis.³²² As noted earlier, using a drug for an off-label use can also complicate the question of who pays for it, as both public and private insurers may be less likely to cover off-label uses. Nevertheless, the mere formal availability of the drug generally makes access to treatment easier. Tuberculosis is another Neglected Disease whose treatment has frequently involved off-label use.³²³ Many off-label uses emerged during the half century during which no novel TB drugs were developed; a number of these off-label uses have since become internationally recognized as part of the standard of care. One example is linezolid, an antibiotic whose use for drug-resistant TB was added to the WHO MEML in 2015; linezolid is available in Canada for other indications, but its increasing use for TB has been off-label.³²⁴ A further example is clofazimine, which has been on the WHO MEML since the inaugural list for treating a different Neglected Disease, leprosy. Subsequently, it also became part of standard regimens for treating drug-resistant tuberculosis; it was added to the WHO MEML for this indication in 2017, despite the fact that it was not approved for the treatment of tuberculosis by any

³²¹ Chiu, Stephanie & Charlene Argaez, *Ivermectin for Parasitic Skin Infections of Scabies: A Review of Comparative Clinical Effectiveness, Cost-Effectiveness, and Guidelines*, CADTH Rapid Response Reports (Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, 2019).

³²² Manciuilli, Tommaso et al., "Shortage of Albendazole and Its Consequences for Patients with Cystic Echinococcosis Treated at a Referral Center in Italy" (2018) 99:4 Am J Trop Med Hyg 1006–1010.

³²³ Tiberi, S et al., "New drugs and perspectives for new anti-tuberculosis regimens" (2018) 24:2 Pulmonology 86–98, online: <<https://linkinghub.elsevier.com/retrieve/pii/S2173511517301690>>.

³²⁴ Edwards, Brett D et al., "Rifampin-resistant/multidrug-resistant Tuberculosis in Alberta, Canada: Epidemiology and treatment outcomes in a low-incidence setting" (2021) 16:2 PLoS ONE e0246993, online: <<https://dx.plos.org/10.1371/journal.pone.0246993>>.

Stringent Regulatory Authority.³²⁵ Even before a TB indication was added to the WHO MEML, however, clofazimine was already included in the Public Health Agency of Canada-endorsed *Canadian Tuberculosis Standards* for the treatment of drug-resistant TB.³²⁶ Nevertheless, despite its longstanding use in Canada and elsewhere, clofazimine still lacks Health Canada approval for any indication whatsoever; instead, it is only obtainable through the SAP. This means that requesting clofazimine for the treatment of DR-TB via the SAP – which has been expressly highlighted in Canada’s own guidelines as the only route to obtain this recommended medicine – involves requesting a drug for an off-label indication.³²⁷ Requesting access to an unmarketed drug for an off-label indication – even one that is found on the WHO MEML and in national treatment guidelines– can complicate the access process further.

Ultimately, because there is no commercial interest in selling drugs like clofazimine in Canada, they do not receive approval from Health Canada, which in turn keeps them out of the physician’s official toolbox, whether for their approved indications or off-label for other conditions. That physicians face greater restrictions in accessing Essential Medicines that constitute the global standard of care yet are unavailable in Canada than they do for using less established but formally approved drugs for an unapproved purpose at their own discretion further illustrates how regulatory goals around safety and efficacy do not necessarily lead to the safest and most efficacious outcomes for patients.³²⁸ The ability to access Essential Medicines for off-label purposes that are nonetheless

³²⁵ WHO Expert Committee on the Selection and Use of Essential Medicines, ed, *The selection on use of essential medicines: report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children)*, WHO technical report series 1006 (Geneva: WHO, 2017) at p.151.

³²⁶ Long, Richard, Monica Avendano & Dennis Kunimoto, “Chapter 8: Drug-Resistant Tuberculosis” in *Canadian Tuberculosis Standards*, 7th ed. ed (Public Health Agency of Canada, 2014) at p.18.

³²⁷ Long, Richard, Monica Avendano & Dennis Kunimoto, “Chapter 8: Drug-Resistant Tuberculosis” in *Canadian Tuberculosis Standards*, 7th ed. ed (Public Health Agency of Canada, 2014) at p.18. This has been reaffirmed in the updated 8th edition, released as this thesis was being finalized. Brode, Sarah K et al., “Chapter 8: Drug-resistant tuberculosis” (2022) 6:sup1 Canadian Journal of Respiratory, Critical Care, and Sleep Medicine 109–128, online: <<https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2039499>>.

³²⁸ For the third element of the regulatory triumvirate, quality, Health Canada approval does still broadly yield the same benefits whether the drug is used on or off-label.

recognized as the standard of care is a further reason why formal availability, rather than a simple expansion of informal availability, is to be preferred.

Chapter 3: Accessing unapproved drugs in Canada

Modes of access

As should be clear at this point, the fact a drug does not have market approval in Canada does not mean that it is not of medical importance, or that there are no patients who would benefit from access to it. While Essential Medicines are a particularly salient example, there are also a wide range of other drugs, both old and new (and, as will be seen, of varying utility), that are in demand despite not being formally available. In turn, although Canada's regulatory system is premised upon guarding against unsafe, ineffective or poor-quality drugs, rather than enticing market entry for medically useful ones, it has long recognized that there are circumstances in which a medicine not formally available in Canada may need to be accessed. Generally speaking, however, the resulting measures have been intended as temporary stopgaps, rather than the long-term, and indeed *de facto* permanent, access pathways they have become in some cases. There are three primary ways of accessing unmarketed drugs in Canada. First, there are clinical trials. Second, there is self-importation from abroad. Finally, there are legal mechanisms which permit the importation of unapproved drugs for the treatment of patients. The most important and longstanding mechanism within this third group is one frequently foreshadowed thus far, the Special Access Programme (SAP), which will form the primary focus of this discussion. Even a cursory examination of these pathways makes it clear that they have not been designed with standard of care drugs such as decades-old off-patent Essential Medicines for Neglected Diseases in mind.

Clinical trials

The first method of obtaining access to an unmarketed medicine in Canada is to participate in an clinical trial using that drug.³²⁹ For some classes of conditions, such as Rare Diseases, that have relatively few treatments with longstanding

³²⁹ This can be a complicated process. See e.g., Health Canada, "Guidance for completing the Drug Submission Application Form" (31 March 2021), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/forms/guidance-completing-drug-submission-application-form.html>>.

approval anywhere in the world and a comparatively large number of treatments currently in development, clinical trials access is a major consideration; indeed, pharmaceutical companies have used removing clinical trials from Canada as leverage when opposing other regulatory reforms, such as measures to reduce drug prices.³³⁰ For off-patent Essential Medicines for Neglected Diseases, however, access via Canadian clinical trials is likely to be relatively rare. Quite aside from general disinterest in bringing these drugs to the Canadian market, the fact that these drugs are often relatively well understood as a result of years of clinical use as the standard of care, combined with a relative dearth of Canadian patients to participate in a clinical trial compared to countries where such diseases are more prevalent, all help to explain why few clinical trials for such drugs occur in Canada.³³¹ As such, while experimental trials may be an important means of accessing certain unmarketed drugs in the short term, generally speaking they are neither particularly feasible nor appropriate for Essential Medicines already established as the standard of care. As a result, clinical trials will not be the subject of further discussion. It is nonetheless worth pointing out, however, that other countries similarly grappling with the need to access Essential Medicines nobody wants to bring to market have leaned more heavily on this approach, using the premise of clinical trials as the primary regulatory workaround to provide access to unmarketed Essential Medicines for Neglected Diseases in the absence of an effective mechanism for bringing the drugs into the formal market.³³²

Self-importation

Another method of access in Canada is self-importation. Legally, importation of a prescription medication by someone who is not a practitioner, drug manufacturer,

³³⁰ For an example of this being raised in opposition to reforms to the Patented Medicine Prices Review Board (PMPRB), see Life Sciences Ontario, “Impact of PMPRB Pricing Changes Final Research Report” (3 February 2020), online: <<https://lifesciencesontario.ca/wp-content/uploads/2020/02/Research-Etc.-PMPRB-Survey-02-03-20.pdf>>.

³³¹ That said, it should be acknowledged that there are certainly exceptions, especially for endemic conditions like tuberculosis. See e.g., this trial involving rifapentine: Pease, C, K R Amaratunga & G G Alvarez, “A shorter treatment regimen for latent tuberculosis infection holds promise for at-risk Canadians” (2017) 43:3–4 Can Commun Dis Rep 67–71.

³³² The method of using n=1 trials is discussed in relation to accessing off-patent Essential Medicines for Neglected Diseases in the United States elsewhere in this thesis.

wholesale druggist or pharmacist is restricted to “a resident of a foreign country while a visitor in Canada”.³³³ As such, Canadian residents are technically not permitted to freely import such drugs. If imported, such drugs may be confiscated and disposed of by an officer under the *Customs Act*.³³⁴ However, as a matter of discretion, Health Canada notes that it may permit a Canadian resident to import a short-term supply (up to ninety days) of an unapproved medicine into Canada for personal use under certain circumstances, such as when treatment was initiated abroad.³³⁵ A similar approach is taken toward recent immigrants and refugees continuing treatment.³³⁶ This serves as a reminder that for some of the Neglected Diseases discussed in this thesis, including malaria and a range of other parasites, a patient arriving from elsewhere will often have readier access to superior therapies – perhaps even funded by a Canadian initiative – if they seek treatment in the country where infection occurred rather than waiting until arrival in Canada.³³⁷ As noted earlier, in the case of malaria, continuation of treatment initiated abroad with a superior drug unmarketed in Canada is a sufficiently widespread practice that it is explicitly incorporated into Canada’s treatment guidelines.³³⁸

³³³ C.01.045 Food and Drug Regulations (C.R.C., c. 870).

³³⁴ S.101-102, *Customs Act* (R.S.C., 1985, c. 1 (2nd Supp.))

³³⁵ Health Canada, “Bringing health products into Canada for personal use (GUI-0116)” (23 December 2020), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/importation-exportation/personal-use-health-products-guidance/document.html>>.

³³⁶ Health Canada, “Bringing health products into Canada for personal use (GUI-0116)” (23 December 2020), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/importation-exportation/personal-use-health-products-guidance/document.html>>.

³³⁷ As this thesis was being finalized, the author was engaged in discussions around continuity of care for refugees from Ukraine with drug-resistant tuberculosis. Ukraine has high levels of drug-resistant TB; however, Essential Medicines employed in the Ukrainian response, including old drugs like clofazimine and cycloserine and new drugs like bedaquiline are not formally available in some countries receiving refugees, including Canada, despite being procured in Ukraine via the Canadian-sponsored Global Drug Facility (GDF), discussed later. See e.g., Ravelo, Jenny Lei, “WHO, Stop TB seek permits for MDR-TB medicines for Ukraine refugees”, *Devex* (24 March 2022), online: <<https://www.devex.com/news/who-stop-tb-seek-permits-for-mdr-tb-medicines-for-ukraine-refugees-102918>>.

³³⁸ Committee to Advise on Tropical Medicine and Travel & Public Health Agency of Canada, “Chapter 7 - Treatment of malaria: Canadian recommendations for the prevention and treatment of malaria” in Canadian recommendations for the prevention and treatment of malaria – CATMAT (Updated 2019), online: <<https://www.canada.ca/en/public-health/services/catmat/canadian-recommendations-prevention-treatment-malaria/chapter-7-treatment.html>>.

Questions around the limits of self-importation have been considered by the courts, occasionally intersecting with other access methods such as the Special Access Programme, as in the 2014 case of *Patel v Canada (Citizenship and Immigration)*.³³⁹ In that case, an individual attempted to sponsor his mother, who was HIV-positive, as a family class migrant from India. Because of the costs of HIV treatment, it was determined his mother might reasonably be expected to put “excessive demand” on health and social services, and the application was denied.³⁴⁰ The appeal argued that the family would avoid these costs in one of two ways. The first was by regular trips to India to import the drug for personal use. The second was by accessing an Indian version of the medicine, which was unapproved in Canada but considerably cheaper, via the SAP. However, the court found neither of these pathways would be feasible.³⁴¹ As this decision suggests, and as reinforced by the practicalities of regular travel to take advantage of Health Canada’s discretionary approach to otherwise illegal short-term importation,

³³⁹ *Patel v Canada (Citizenship and Immigration)*, 2014 CanLII 83187 (CA IRB).

³⁴⁰ While beyond the scope of this thesis, medical inadmissibility has longstanding links to Neglected Diseases. Amendments to the *Immigration Act* in 1902 prohibited the landing of passengers “suffering from any loathsome, dangerous or infectious disease or malady” (*An Act to amend the Immigration Act*, R.S.C. 65, 2 E. VII, c. 14, s.24). This would actually predate the better-known amendments of 1906, which further excluded potential migrants on cultural grounds. The restrictions on infectious disease encompassed Neglected Diseases like TB, while trachoma was for years the primary cause for rejection. Vineberg, Robert, “Healthy Enough to Get In: The Evolution of Canadian Immigration Policy Related to Immigrant Health” (2015) 16:2 Int Migration & Integration 279–297, online: <<http://link.springer.com/10.1007/s12134-014-0339-3>>; see also Byers, W Gordon M, “Trachoma in Canada” (1932) 27:4 Can Med Assoc J 372–376. By mid-Century, tuberculosis and trachoma would remain singled out by name in the *Immigration Act*; persons with either disease belonged to a prohibited class. *Immigration Act*, R.S.C. 1952, c. 325, s.5(b). Today, diseases are no longer singled out quite so blatantly by name, but a foreign national may still be inadmissible on health grounds if their health condition (a) is likely to be a danger to public health; (b) is likely to be a danger to public safety; or (c) might reasonably be expected to cause excessive demand on health or social services. *Immigration and Refugee Protection Act* S.C. 2001, c. 27 s.38(1). Medical examinations for conditions like TB may still be required for many prospective migrants. In recent decades, as it did with access to medicines, HIV gradually became the centre of attention for immigration restrictions; as illustrated in *Patel*, this has largely focused on the cost of treatment serving as a barrier for certain classes of migrant. Fortunately, there has been recent improvement in this regard, including tripling the financial threshold. See e.g., Immigration, Refugees and Citizenship Canada, “Government of Canada brings medical inadmissibility policy in line with inclusivity for persons with disabilities” (16 April 2018), online: <<https://www.canada.ca/en/immigration-refugees-citizenship/news/2018/04/government-of-canada-brings-medical-inadmissibility-policy-in-line-with-inclusivity-for-persons-with-disabilities.html>>.

³⁴¹ *Patel v Canada (Citizenship and Immigration)*, 2014 CanLII 83187 (CA IRB). The SAP cannot generally be used to import an unapproved version of a drug when an approved version is available.

personal importation is not an effective systemic solution for access to unmarketed Essential Medicines in Canada, even as it illustrates some of the incongruities in global access.

Special Access Programme (SAP)

For decades, the Special Access Programme (SAP) has been the primary mode of access to unmarketed drugs in Canada.³⁴² It is a long-standing mode of access, with an underlying regulatory framework created in 1966.³⁴³ This regulatory chassis remained largely unchanged for over fifty years, even as the programme changed names; the predecessor of the Special Access Programme, underpinned by those same regulations, was the Emergency Drug Release Programme (EDRP), which was in place from the mid-1960s until the mid-1990s.³⁴⁴ Only very recently, as discussed later in this thesis, have notable changes been made to the underlying regulations themselves.³⁴⁵ However, the SAP continues to create additional hurdles between the patient and the medicine that would not exist were the medicine formally available in Canada.

The SAP draws its authority from sections C.08.010 and C.08.011 of the *Food and Drug Regulations*. The heading for this section of the *Regulations* is an apt description of the goals of the SAP: “Sale of New Drug for Emergency Treatment”. Consider an idealized example of a scenario the SAP is meant to address: A novel cancer drug has just been approved in a (larger, more lucrative) market like the US or the EU, but is still in the midst of the approval process in Canada; the SAP is used to access this as-yet unapproved drug for a Canadian patient whose life is in danger, for whom all other treatment options have failed, and who cannot wait for the approval process to be completed in order to obtain formal access.³⁴⁶ In other

³⁴² The Government of Canada is inconsistent in its usage of Special Access Programme vs. Special Access Program. The author has traditionally used the former, and thus will aim for consistency.

³⁴³ “Food and Drug Regulations, amended”, *Canada Gazette, Part II*, Vol.100, no. 22, (23 November 1966) p.517-518.

³⁴⁴ Given the consistency of the underlying regulations, the SAP should be read as including the EDRP, except where clear from context or explicitly noted.

³⁴⁵ The author has advocated for many of these changes since 2015; to foreshadow later discussion, recent reforms are a step in the right direction, but insufficient.

³⁴⁶ The timing here has more to do with companies applying for market approval in the most lucrative markets first rather than Canada’s regulatory system itself being slower. Even a recent

words, it is intended as a bridging mechanism to ensure temporary, emergency access to new drugs during what is, in theory, the brief period between their development and their formal market approval in Canada. Contrast this idealized example with the decades-old Essential Medicines that are the focus of this thesis, and for which the SAP has long been virtually the only method of access, and the shortcomings of the SAP become readily apparent.

As mentioned, the regulations underpinning the SAP have very recently undergone some long-awaited (if still insufficient) reforms, the first truly significant reforms in their history. These reforms will be addressed later on. To explore the SAP in detail, it is helpful to begin with the regulations as they looked at the time this thesis was initiated; importantly, with one minor exception, this is also how the regulations looked when first initiated in 1966. As such, the relevant sections of the *Food and Drug Regulations*, read as follows:

Sale of New Drug for Emergency Treatment

- **C.08.010 (1)** The Minister may issue a letter of authorization authorizing the sale of a quantity of a new drug for human or veterinary use to a practitioner named in the letter of authorization for use in the emergency treatment of a patient under the care of that practitioner, if
 - **(a)** the practitioner has supplied to the Minister information concerning
 - **(i)** the medical emergency for which the drug is required,
 - **(ii)** the data in the possession of the practitioner with respect to the use, safety and efficacy of that drug,
 - **(iii)** the names of all institutions in which the drug is to be used, and
 - **(iv)** such other data as the Minister may require; and
 - **(b)** the practitioner has agreed to
 - **(i)** report to the manufacturer of the new drug and to the Minister on the results of the use of the drug in the medical emergency,

report from the oft-Health Canada-averse Fraser Institute found that delays in Canadian approval were driven almost entirely by the date companies submitted the drugs for approval, rather than a slower regulatory process. Late submissions accounted for 464 of the average 468-day gap between American and Canadian approval, and 395 days of the average 404-day gap between the EU and Canada. Barua, Bacchus, Will Westcott & Van Nghiem Vo, *Timely Access to New Pharmaceuticals in Canada, the United States, and the European Union* (2021, Fraser Institute).

- including information respecting any adverse reactions encountered, and
 - **(ii)** account to the Minister on request for all quantities of the drug received by him.
- **(1.1)** The Minister shall not issue a letter of authorization under subsection (1) for a new drug that is or that contains a restricted drug as defined in section J.01.001.³⁴⁷
- **(2)** The Minister shall, in any letter of authorization issued pursuant to subsection (1), state
 - **(a)** the name of the practitioner to whom the new drug may be sold;
 - **(b)** the medical emergency in respect of which the new drug may be sold; and
 - **(c)** the quantity of the new drug that may be sold to that practitioner for that emergency.
- **C.08.011 (1)** Notwithstanding section C.08.002, a manufacturer may sell to a practitioner named in a letter of authorization issued pursuant to section C.08.010, a quantity of the new drug named in that letter that does not exceed the quantity specified in the letter.
- **(2)** A sale of a new drug made in accordance with subsection (1) is exempt from the provisions of the Act and these Regulations.

While this section of the *Act* also applies to veterinary drugs, the focus of this thesis will be solely on human patients; however, it is worth remembering that for some of the drugs under discussion, vets have long had superior access, with veterinary formulations of drugs like ivermectin available in Canada decades before a product for humans. What follows is a brief overview of the typical SAP application process, and hurdles that arise at each stage.

Under the SAP, it is the practitioner who submits an application for access to Health Canada; there is no direct role for the patient. This application must be made for each individual patient; the application must include the information required under C.08.010 (1)(a) of the *Regulations*.³⁴⁸ Thus, the practitioner has to

³⁴⁷ Section C.08.010(1.1) is the one revision that occurred between 1966 and 2020; it will be discussed in due course.

³⁴⁸ This is one area where some changes have occurred as a result of recent reforms, discussed later. Previously, a form to request future access met with limited success in practice. Houston, Adam R et al., "Reforming Canada's Special Access Programme (SAP) to improve access to off-patent essential medicines" (2018) 3:2 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 100–107, online: <<http://jammi.utpjournals.press/doi/10.3138/jammi.2018.01.04>>.

submit information and details about the medical emergency.³⁴⁹ Herein lies one hurdle for access; “medical emergency” is not defined in the regulations, though it has been interpreted by Health Canada in practice as meaning “serious or life-threatening”.³⁵⁰ Unfortunately, this has left some Canadian patients in need of Essential Medicines without proper treatment. Consider the Neglected Disease cutaneous larva migrans, which has exemplified the gap in the ability to access medicines that constitute the recognized standard of care via the SAP.³⁵¹ Cutaneous larva migrans is not a life-threatening condition; it is, however, an intensely itchy and unpleasant experience for the patient. In turn, the unmarketed Essential Medicines used to treat this condition – albendazole and ivermectin – were for decades available only under the SAP; while ivermectin has finally been brought to market in Canada, this remains the case for albendazole.³⁵² Unfortunately, in many cases the physician’s request to the SAP for drugs to treat cutaneous larva migrans has been declined, as the medical condition was not deemed sufficiently “serious” to qualify as a medical emergency. This is precisely what transpired for the couple encountered earlier in this thesis who came home from the Dominican Republic with cutaneous larva migrans in their feet.³⁵³ Instead, Canadian patients have historically been prescribed ineffective courses of non-targeted therapy, an approach that makes a poor use of health system resources while providing

³⁴⁹ S. C.08.010 (1)(a)(i).

³⁵⁰ Health Canada, Special access program for drugs : guidance document for industry and practitioners (Revised 2022), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/special-access/drugs/guidance/sap-drugs-guid-ld-eng.pdf>> at p.8.

³⁵¹ Strictly speaking a manifestation of a Neglected Disease. Cutaneous larva migrans is a condition in which a species of hookworm not adapted to a human host (e.g., a hookworm whose host is another animal, such as a dog) enters the human body but is unable to complete its normal lifecycle as it would in its natural host, and instead stays in the cutaneous layer.

³⁵² Houston, Adam R et al., “Reforming Canada’s Special Access Programme (SAP) to improve access to off-patent essential medicines” (2018) 3:2 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 100–107, online: <<http://jammi.utpjournals.press/doi/10.3138/jammi.2018.01.04>>.

³⁵³ Chen, Dalson. “Caribbean vacation turns into parasite nightmare for Windsor couple”, *Windsor Star* (26 January 2018), online: <<https://windsorstar.com/news/local-news/caribbean-vacation-turns-into-parasite-nightmare-for-windsor-couple>>.

minimal benefit to the patient.³⁵⁴ Contrast this to the considerable leeway provided to a physician using a medicine that has formal approval in Canada, even for a completely different indication; now that ivermectin is formally marketed in Canada, a physician could prescribe it off-label (it is not indicated in Canada for cutaneous larva migrans), regardless of the fact the condition would not be classified as a serious or life-threatening medical emergency.

Next, the application has to include “information in the possession of the practitioner with respect to the use, safety and efficacy of the drug”.³⁵⁵ When using the prescribed form in responding to these questions, the practitioner is directed to “provide specific information about your patient(s)’s medical history including conventional therapies considered, ruled out and/or failed or that are unsuitable and/or unavailable to achieve an adequate response” and to answer the question “What specifically about this drug (e.g. mechanism of action, drug class, dosage form) makes it the best choice for your patient(s)’s?”³⁵⁶ In support of this request, the physician is directed to “Please provide SPECIFIC data, references and/or resources in your possession, with respect to the use, safety and efficacy that support your decision to prescribe this drug,” including journal citations.³⁵⁷

For a physician using a novel cancer treatment, perhaps even one that has yet to be approved anywhere in the world, providing this level of detail seems *prima facie* a reasonable balance to ensure the safety of the patient, given the relative lack of knowledge of and experience with the drug. For a physician using a drug approved elsewhere with decades of clinical use behind it, and recommended in both Canadian and international guidelines as the standard of care, the burden

³⁵⁴ Kincaid, Leah et al., “Management of imported cutaneous larva migrans: A case series and mini-review” (2015) 13:5 Travel Medicine and Infectious Disease 382–387, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1477893915001222>>.

³⁵⁵ S. C.08.010 (1)(a)(ii).

³⁵⁶ This brief overview does not explore every historical tweak to the application form; instead, by way of example, it focuses on the form commonly used for most of the past decade as a general overview. Health Canada “Form A – Patient Specific Request” (Revised 2008), online: <https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/acces/sapf1_pasf1-eng.pdf>.

³⁵⁷ Emphasis in original. Health Canada “Form A – Patient Specific Request” (Revised 2008), online: <https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/acces/sapf1_pasf1-eng.pdf>.

imposed does not similarly correspond to the resulting benefit to patient safety. Nevertheless, such information has generally had to be provided with every request for every patient, no matter how many times a request had been submitted for the same drug to treat the same condition in the past. If anything, this disjunct in terms of the “need” for safety and efficacy information underscores how poorly long-used Essential Medicines forming the standard of care fit within the longstanding SAP framework.

Complicating matters further, off-patent Essential Medicines for Neglected Diseases may be especially prone to facing challenges in meeting these requirements under the SAP. As outlined in a submission to recent Health Canada consultations, there have been instances of standard of care treatments being rejected on the grounds of “lack of recent literature” because the supporting literature was more than five years old; as the submission notes, for some uncommon conditions, especially infectious diseases, the current standard is based on studies older than five years, and new literature simply doesn’t exist.³⁵⁸ The consequence is that an Essential Medicine established as the standard of care for decades might counterintuitively face a higher risk of rejection simply because its utility has been established for a longer period of time. This is not the only piece of information that may pose difficulties. For instance, the physician must also provide information about the manufacturer of the drug, a piece of information the individual physician is not always the best positioned to ascertain, especially in cases – like a number of those discussed in this thesis – where ownership of a long-used source has recently changed, or prices from a traditional source have drastically increased to the point the drug is financially inaccessible.³⁵⁹

After the application has been submitted, Health Canada decides whether to issue a letter of authorization, decline to do so, or ask for more information before

³⁵⁸ Canadian Society of Hospital Pharmacists, “Health Canada’s Consultation on SAP Renewal” (2018), online: <<https://cshp.ca/sites/default/files/2019-05/Health%20Canada%27s%20Consultation%20on%20SAP%20Renewal%20-%20CSHP%20Response%20Jan%2718.pdf>> at para. 26.

³⁵⁹ Health Canada “Form A – Patient Specific Request” (Revised 2008). Online: <https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/acces/sapf1_pasf1-eng.pdf>.

deciding. As this author and his colleagues have detailed elsewhere, this decision-making process is an opaque one; medicines being requested by specialists in particular medical disciplines can be turned down for unclear reasons by assessors of unknown qualifications.³⁶⁰ Most importantly, even where all the steps are followed, the SAP has not proven an efficient tool for gaining timely access to Essential Medicines. Although the SAP's stated aim has been to process most requests within 24 hours of receipt, this has frequently not been the experience of physicians requesting off-patent Essential Medicines for Neglected Diseases in recent years.³⁶¹ This has been true even where the initial request is accepted; if it is initially declined, or if the SAP requests additional information, the process can take even longer.³⁶² For a mechanism explicitly intended for emergency treatment for a condition that is serious or life-threatening, such delays pose potentially major risks to the patient.

Furthermore, even a successful application resulting in the issuance of a letter of authorization from Health Canada does not ensure the drug reaches the patient. Health Canada does not provide the drug itself; it merely removes legal restrictions on the physician obtaining it from the manufacturer. As such, all the letter does is that it authorizes the sale of the specified amount of drug to the practitioner named in the letter. The manufacturer is under no obligation to provide the drug. They can accept or refuse as per their wont, and are not obliged to offer any explanation for their decision.³⁶³ And even if the drugmaker agrees to

³⁶⁰ Houston, Adam R et al., "Reforming Canada's Special Access Programme (SAP) to improve access to off-patent essential medicines" (2018) 3:2 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 100–107, online: <<http://jammi.utpjournals.press/doi/10.3138/jammi.2018.01.04>>.

³⁶¹ This will be demonstrated in more detail shortly.

³⁶² Houston, Adam R et al., "Reforming Canada's Special Access Programme (SAP) to improve access to off-patent essential medicines" (2018) 3:2 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 100–107, online: <<http://jammi.utpjournals.press/doi/10.3138/jammi.2018.01.04>>.

³⁶³ Here the lack of tangible public data on the SAP is once again a barrier, as statistics on manufacturer refusal are not readily available. However, the author observes that it is seldom raised in the literature about off-patent Essential Medicines for Neglected Diseases, and while numerous physicians have indicated informally to the author that it does occur, none have suggested it was a primary barrier to access. Things may be different for other medicines obtained via the SAP; certainly, one can easily imagine scenarios where a company actively attempting to bring a new drug to market might be reluctant to have it used under less-than-ideal circumstances, lest it

supply their drug, there remains the question of the cost of that drug, an issue where, as will be seen, off-patent drugs fall through the cracks of Canada's regulatory system.

Finally, each successful request is granted for a limited period of a few months, following which another application is necessary.³⁶⁴ For drugs patients must use in perpetuity – such as many Rare Disease drugs, discussed in more detail later, but also in some cases drugs for Neglected Diseases like strongyloidiasis – such renewals are not merely unnecessarily onerous, but make a mockery of the idea of a medical emergency. And for conditions such as drug-resistant tuberculosis that urgently require a period of treatment longer than six months, a time limit ensures at least one additional request must be made, raising the threat of treatment interruption, and with that, the spectre of the development of yet further drug resistance. In such cases, the time limit imposes not merely a bureaucratic burden but, in some cases, a potential risk to both the patient and to public health.

Impacts of the SAP on Essential Medicine for Neglected Diseases

The barriers imposed by the SAP as outlined above are not hypothetical. They have tangible impacts on patient care. Before proceeding, it is of course worth reiterating that a drug obtained via the SAP is still unapproved, even in those instances where it forms the acknowledged standard of care. This means it has not formally met Health Canada's standards for safety, efficacy and quality. Courts have recognized that "it is theoretically possible that drugs available under the Special Access Programme are not entirely safe or effective".³⁶⁵ Indeed, such safety questions around drugs obtained via the SAP do arise in practice.³⁶⁶ This is also a

damage the incoming new drug's reputation. Supporting this idea, issues of refusal have been documented more frequently in the United States in conjunction with access to investigational drugs outside of clinical trials. See e.g., Walker, Scot, "Expanded Access Versus Right-to-Try" (2020) 55:2 Hosp Pharm 79–81.

³⁶⁴ This is one more aspect implicated in recent reforms, as will be revisited.

³⁶⁵ *Teva Canada Limited v. Canada (Health)*, 2012 FCA 106 at para. 28.

³⁶⁶ For instance, drugs obtained via the SAP may raise concerns about drug interactions. See e.g., Atkinson, Suzanne et al., "Risk of Drug Interactions among Children Accessing Drugs through Health Canada's Special Access Programme" (2007) *The Canadian Journal of Hospital Pharmacy* 60:2.

reason why principles around informed consent still apply.³⁶⁷ Such potential risks also justify why the requesting practitioner is required to report adverse effects. At the same time, this requirement also serves to demonstrate Canada's pick-and-choose approach to international standards for pharmaceuticals in other ways. For instance, Canada has adopted International Conference of Harmonization (ICH) guidelines as the standard for ADR [Adverse Drug Reaction] reporting under the SAP, "both in regards to what should be reported and the associated timeframes".³⁶⁸ As seen later on, similar standards have not been so readily applied when it comes to recognizing foreign approval of Essential Medicines in the first place.

While the potential risks of unapproved drugs accessed via the SAP are not a purely hypothetical concern, the processes of the SAP have imposed a real barrier to meeting the national and global standards of care for patients with Neglected Diseases. Consider tuberculosis. Cycloserine, as the reader is by now aware, is an Essential Medicine for drug-resistant tuberculosis. Internationally, its global importance as a treatment for drug-resistant TB was reaffirmed in 2020 in the newly revised *WHO consolidated guidelines on drug-resistant tuberculosis treatment*.³⁶⁹ It is also recommended in the 2022 edition of the *Canadian Tuberculosis Standards*, the official guidelines published by Canadian Thoracic

³⁶⁷ There is little legal exploration of this issue in the context of the SAP. The discrepancies between explicit regulatory requirements around ethics approval and informed consent in the context of clinical trials but not for drugs accessed via the SAP are flagged by von Tigerstrom and Harris. They further highlight that additional requirements may exist at the provincial or local level. Tigerstrom, Barbara von & Emily Harris, "Access to Experimental Treatments: Comparative Analysis of Three Special Access Regime" (2016) 24 *Journal of Law and Medicine* 119–149. The nearest the issue has come to exploration in the courtroom is in a case where a complaint was made to the College of Physicians & Surgeons of British Columbia that a physician had prescribed an "illegal drug" obtained via the SAP. Although the question of consent is not fully resolved, the College upheld the Registrar's dismissal of the complaint on the basis its thrust was the prescription of an illegal drug, stating "It is clear from the Record that [the drug] when obtained through SAP is a legal drug in Canada". *Complainant v. College of Physicians and Surgeons of British Columbia*, 2013 BCHPRB 28 (CanLII), online: <<https://canlii.ca/t/hvsnx>> at para. 14.

³⁶⁸ Health Canada, Special access program for drugs : guidance document for industry and practitioners (Revised 2022), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/special-access/drugs/guidance/sap-drugs-guid-ld-eng.pdf>> at p.19.

³⁶⁹ World Health Organization, *WHO consolidated guidelines on tuberculosis. Module 4*, (2020).

Society with the support of the Public Health Agency of Canada.³⁷⁰ However, because Eli Lilly, the sole company with market authorization in Canada, withdrew cycloserine from the Canadian market for commercial reasons over two decades ago, it has only been accessible as a “new” drug via the SAP since that time.

Unfortunately, cycloserine is the norm rather than the exception when it comes to drug-resistant tuberculosis. Alarming, at the time of the cycloserine price hike, six of eleven drugs listed as second-line drugs for the treatment of drug-resistant tuberculosis in the *Canadian Tuberculosis Standards* were unavailable in Canada.³⁷¹ This is despite the fact that all eleven of them were on the WHO MEML at that time.³⁷² Furthermore, all eleven are off-patent.³⁷³ Navigating the barrier of Essential Medicines not being formally available in Canada is so ingrained within the Canadian response to tuberculosis that the list of recommended drugs was explicitly accompanied by a boxed text stating:

Kanamycin, capreomycin, ethionamide, para-aminosalicylic acid, cycloserine and clofazimine are not available in Canada, except perhaps pursuant to a practitioner's application for treatment of a patient through the Special Access program, available at Health Canada, Drugs and Health Products website.³⁷⁴

³⁷⁰ Brode, Sarah K et al., “Chapter 8: Drug-resistant tuberculosis” (2022) 6:sup1 Canadian Journal of Respiratory, Critical Care, and Sleep Medicine 109–128, online: <<https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2039499>>.

³⁷¹ Long, Richard, Monica Avendano & Dennis Kunimoto, “Chapter 8: Drug-Resistant Tuberculosis” in *Canadian Tuberculosis Standards*, 7th ed. ed (Public Health Agency of Canada, 2014) at p.18 (Table 7).

³⁷² Long, Richard, Monica Avendano & Dennis Kunimoto, “Chapter 8: Drug-Resistant Tuberculosis” in *Canadian Tuberculosis Standards*, 7th ed. ed (Public Health Agency of Canada, 2014) at p.18.

³⁷³ It should be noted that this edition (7th) of the *Standards* did not explicitly include either of the two novel drugs (bedaquiline and delamanid) emerging around the time it was written, although their existence and potential future promise was acknowledged. Furthermore, at the international level, these newer drugs have since displaced some of the older drugs included in the 7th edition; as discussed later, some older drugs, like capreomycin, have been removed from international guidelines and from the WHO MEML itself. Some of these changes are reflected in the 8th edition, released in 2022.

³⁷⁴ Long, Richard, Monica Avendano & Dennis Kunimoto, “Chapter 8: Drug-Resistant Tuberculosis” in *Canadian Tuberculosis Standards*, 7th ed. ed (Public Health Agency of Canada, 2014) at p.18 (Table 7).

The subtle deployment of the word “perhaps” in that statement suggests the presence of some very cynical TB physicians on the drafting committee. This would be unsurprising; underscoring how long accessing unmarketed drugs has been an issue in Canadian tuberculosis care, half of these same TB drugs were similarly described as “emergency drugs” only available in Canada under what was then the EDRP under the same sections of the *Food and Drug Regulations* in 1985.³⁷⁵ Indeed, criticisms of the existing system are more overtly expressed in the 2022 update to the *Canadian Tuberculosis Standards*, in which the authors directly “encourage federal and provincial government agencies and pharmaceutical companies operating in Canada to facilitate timely access to second-line drugs for MDR and XDR-TB by eliminating existing administrative obstacles, such as the requirement for Special Access Program approval for drugs recommended by WHO for drug-resistant TB treatment”.³⁷⁶ The disturbing reality behind such calls for action is that even for drug-resistant tuberculosis – a very serious condition for the patient, and a potential public health disaster for the community – requests for these Essential Medicines via the SAP are not always approved, and are frequently delayed. Given the DR-TB is treated with regimens of multiple drugs, such delays can complicate treatment further. Treatment delay can have serious consequences, even when the drug eventually arrives. Furthermore, these are administrative delays that would not occur for drugs approved in Canada, putting patients with DR-TB at a further disadvantage.

Similar concerns around refusal of requests by the SAP and delayed access for accepted requests have been observed with Essential Medicines for other Neglected Diseases as well. Data obtained by the *Globe and Mail* showed that in 2015, only 78% of requests for ivermectin (498/635) and 76% of cases for

³⁷⁵ White, G.F. & M.J. Davis, “Antiparasitic drugs: availability and regulatory requirements for ‘emergency’ supply” (1985) 132:3 Can Med Assoc J 273–274.

³⁷⁶ Brode, Sarah K et al., “Chapter 8: Drug-resistant tuberculosis” (2022) 6:sup1 Canadian Journal of Respiratory, Critical Care, and Sleep Medicine 109–128, online: <<https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2039499>>.

albendazole (167/220) were successful.³⁷⁷ Once again, this means far fewer patients were able to receive treatment chosen by their physicians than would be the case if the drugs were formally available. Recognizing that refusals and delays are a common but largely unquantified complaint among infectious disease physicians using the SAP, a tropical medicine unit in Toronto, which frequently relies upon the SAP for access to antiparasitic drugs for a diverse clientele, conducted an internal review of their own requests.³⁷⁸ As they describe:

Little information exists to audit parameters of turnaround time or successful applications to SAP for frequently used anti-parasitic medications. Our tracking system was implemented to establish a means to track submissions and ensure receipt of medications to treat common parasitic illnesses encountered in our patient population.³⁷⁹

The authors reiterate the points that despite being recommended in Canadian treatment guidelines some drugs are only available through the SAP, and that resulting delays in access can result in suboptimal patient management or adverse outcomes.³⁸⁰ Focusing solely on albendazole and ivermectin, the authors then review all SAP requests made by practitioners in their unit from 2013-2015. Over those three years, they found:

³⁷⁷ Grant, Kelly, "Why world-beating tropical drugs are so hard to get in Canada", *Globe and Mail* (2 January 2017), online: <<https://www.theglobeandmail.com/news/national/why-world-beating-tropical-drugs-are-so-hard-to-get-incanada/article33469954/>>.

³⁷⁸ Melvin, Rochelle et al. "Evaluation of a clinic-based quality structure for Special Access Programme medicines to treat parasitic infections" (2018) 3:3 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 131-136, online: <<https://jammi.utpjournals.press/doi/10.3138/jammi.2017-0003>>.

³⁷⁹ Melvin, Rochelle et al. "Evaluation of a clinic-based quality structure for Special Access Programme medicines to treat parasitic infections" (2018) 3:3 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 131-136, online: <<https://jammi.utpjournals.press/doi/10.3138/jammi.2017-0003>>.

³⁸⁰ Melvin, Rochelle et al. "Evaluation of a clinic-based quality structure for Special Access Programme medicines to treat parasitic infections" (2018) 3:3 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 131-136, online: <<https://jammi.utpjournals.press/doi/10.3138/jammi.2017-0003>>.

First-time success rates for ivermectin in 2013, 2014, and 2015, respectively, were 96%, 84%, and 71%. First-time success rates for albendazole in 2013, 2014, and 2015, respectively, were 74%, 60%, and 63%. Furthermore, despite non-significance, there was a signal toward increasing initial SAP requests receiving incomplete notifications for both albendazole and ivermectin applications combined over all 3 years.³⁸¹

This study highlights many common problems, from delays in treatment with potentially negative impacts on the patient, to observed changes in SAP responses in practice without clear or transparent justification (for instance, acceptance of requests for albendazole to treat cutaneous larva migrans decreasing over time).³⁸² It must be emphasized once again that these were the outcomes obtained not simply by physicians, but by specialist physicians with considerable experience not only in treating these particular conditions using these specific Essential Medicines, but using the SAP in order to do so.

The standard of care

These examples illustrate a very important concern: that the absence from the Canadian market of drugs that constitute the recognized standard of care inhibits not only the ability of medical experts to provide that standard of care to Canadian patients, but their ability to do so in a timely manner. In fact, delays related to the SAP have been reflected in legal proceedings on meeting the standard of care. Consider the decision of the Health Professions Appeal and Review Board in Ontario in the case of *M.J. v. K.J.* (2018). The decision involved a delay in diagnosis and subsequent treatment of the Neglected Disease Norwegian scabies (crusted

³⁸¹ Melvin, Rochelle et al. "Evaluation of a clinic-based quality structure for Special Access Programme medicines to treat parasitic infections" (2018) 3:3 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 131–136, online: <<https://jammi.utpjournals.press/doi/10.3138/jammi.2017-0003>>.

³⁸² Melvin, Rochelle et al. "Evaluation of a clinic-based quality structure for Special Access Programme medicines to treat parasitic infections" (2018) 3:3 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 131–136, online: <<https://jammi.utpjournals.press/doi/10.3138/jammi.2017-0003>>.

scabies). This delay in treatment ultimately led to the death of the patient. Part – though it must be noted not all – of the failure to provide appropriate treatment in time came via the delay in accessing ivermectin via the SAP.³⁸³ While in this case it was determined the physician did fall short in treating the patient, it was also noted that the SAP forms were submitted on April 20th, and approval not granted until April 27.³⁸⁴ This is well beyond the target of 24hrs. Furthermore:

The infectious disease specialist who finally saw the patient in April 2016 explained to the Committee that he was very troubled by the delays he himself experienced and the “cumbersome” application process that frustrated his efforts. He noted that the ivermectin may not have averted the spread of infection at that stage anyway nor could other practitioners have had any more success in obtaining it than he did.³⁸⁵

As such, the delay in access via the SAP did not ultimately absolve the treating physician of responsibility for the substandard care that led to the death of the patient, but was nevertheless identified as a troubling matter that might have happened to any practitioner, including a specialist with experience using the SAP. As this case – and the information already presented in this section – suggest, the SAP has real impact on the ability to provide Canadian patients timely access to the appropriate standard of care, if they ultimately receive it at all.

³⁸³ *M. J. v K. J.*, 2018 CanLII 109611 (ON HPARB) at para.39-40.

³⁸⁴ *M. J. v K. J.*, 2018 CanLII 109611 (ON HPARB) at para.9-10.

³⁸⁵ *M. J. v K. J.*, 2018 CanLII 109611 (ON HPARB) at para.45.

Chapter 4: Market entry and the SAP

The goals of the SAP

As outlined earlier, the SAP has long been the primary means of access to unmarketed Essential Medicines for Neglected Diseases. In practice, however, it covers a far broader range of drugs. According to Health Canada, the SAP currently receives over 16,000 requests each year.³⁸⁶ In a normal year, around 500 different drugs will be requested.³⁸⁷ This high volume of requests is not new. In 1993, Gilron observed that since its inception, the program had “released over 600 essential drugs before their approval for sale in Canada, and approximately 900 Canadian physicians use the program in any given month”.³⁸⁸ Then as now, many of these requests are for those drugs the SAP was intended for: drugs that are somewhere in the process of receiving formal marketing approval in Canada, but are not there yet. Indeed, the government has noted for decades that “the assumption is that manufacturers will file” for approval.³⁸⁹ The problem is that this assumption has proven incorrect for certain drugs, including numerous drugs for Neglected Diseases, for whom this temporary state of affairs has stretched out for years or even decades, and which may never be brought to market at all under the current regulatory system.

That a mechanism intended as a temporary pathway for emergency access has become a permanent access mechanism for drugs of recognized importance is a flaw with impacts that go beyond the delays and refusals of individual requests. This unhappy state of affairs exists because in most instances there has been no

³⁸⁶ “Regulations Amending Certain Regulations Made Under the Food and Drugs Act (Sale of a New Drug for Emergency Treatment): SOR/2020-212” Canada Gazette, Part II, Volume 154, Number 21 (28 September 2020), online: <<http://www.gazette.gc.ca/rp-pr/p2/2020/2020-10-14/html/sor-dors212-eng.html>>.

³⁸⁷ “Regulations Amending Certain Regulations Made Under the Food and Drugs Act (Sale of a New Drug for Emergency Treatment): SOR/2020-212” Canada Gazette, Part II, Volume 154, Number 21 (28 September 2020), online: <<http://www.gazette.gc.ca/rp-pr/p2/2020/2020-10-14/html/sor-dors212-eng.html>>.

³⁸⁸ Here Gilron appears to be using “essential” in the sense of important, rather than with reference to a formal international or domestic set of Essential Medicines. Gilron, I. “The Emergency Drug Release Program: regulatory aspects of new drug access in Canada” (1993) 148:7 CMAJ 1151–1153.

³⁸⁹ Clark, Edie & Canadian Coordinating Office for Health Technology Assessment, *A Survey of investigational new drug and emergency drug release policies* (Ottawa, Ont.: Canadian Coordinating Office for Health Technology Assessment, 1991) at p.4.

alternative for obtaining access to drugs that the market has failed, whether they have been discontinued or never introduced in the first place. An unusually forthright “Special Access Programme Issue Identification Paper” released by Health Canada in 2007 acknowledges that the SAP “was originally intended to consider requests for drugs that are not yet approved for sale by Health Canada” but has since expanded in scope to encompass additional categories of drugs.³⁹⁰ One of these additional categories is “Discontinued and Withdrawn Drugs”, where the former “are those that have been approved for marketing and have been available for sale but are currently not offered for sale on the Canadian market, typically for economic reasons”.³⁹¹ Cycloserine, pyrimethamine and now chloroquine all fit this bill. Another is “Drugs used by small populations”.³⁹² The description of this category explicitly recognizes medicines for Neglected Diseases:

These are drugs that are not approved for marketing in Canada and regulatory approval is unlikely to be pursued. They are indicated for rare conditions or for a small population and are, therefore, not commercially viable. These drugs may or may not have been approved in other countries. *An example in this category includes drugs used to treat tropical diseases.* Overall, these drugs make up a small component of the drugs requested through the SAP. [*emphasis added*].³⁹³

As this suggests, these issues have been recognized for a long time. They have just never been effectively addressed. At the same time, it also serves as a regulatory

³⁹⁰ Bureau of Policy, Science and International Programs, Special Access Programme Working Group, *Special Access Programme Issue Identification Paper* (Health Canada Therapeutic Products Directorate, 2007) at p.9.

³⁹¹ Bureau of Policy, Science and International Programs, Special Access Programme Working Group, *Special Access Programme Issue Identification Paper* (Health Canada Therapeutic Products Directorate, 2007) at p.9.

³⁹² Bureau of Policy, Science and International Programs, Special Access Programme Working Group, *Special Access Programme Issue Identification Paper* (Health Canada Therapeutic Products Directorate, 2007) at p.9.

³⁹³ Bureau of Policy, Science and International Programs, Special Access Programme Working Group, *Special Access Programme Issue Identification Paper* (Health Canada Therapeutic Products Directorate, 2007) at p.9-10.

dead-end when it comes to formal approval. Access via the SAP is not designed to be complementary to formal approval, but rather as an exception sitting outside the regulatory approval process entirely. At a policy level it has long been explicit that access under the SAP, even if widespread, does not qualify as formal regulatory approval, and cannot be used to establish safety and efficacy.³⁹⁴ From a broader regulatory perspective, such an approach seems appropriate; preventing drug companies from circumnavigating formal review processes to sell their wares (and potentially sell unsafe, ineffective, or low-quality drugs in the process) is a logical goal.³⁹⁵ However, this approach also maintains barriers to the formal approval of drugs whose medical value outweighs their commercial value in a system dependent on commercial interest.

A major deficiency of the existing system has long been that it allows useful but commercially unappealing drugs to exist in regulatory limbo, with some level of patient access premised on potentially unpredictable applications to the SAP, rather than the straightforwardness of access to an approved drug. This is perpetuated by the fact that Health Canada lacks any formal mechanism to remedy this situation. As Health Canada has acknowledged with particular reference to long-term access via the SAP, “Health Canada has no authority to compel a manufacturer to conduct a clinical trial or submit a new drug submission”.³⁹⁶ In the same context, Health Canada has also stated that when it comes to the SAP, it “has no authority to give consideration to other factors that are relevant to a decision on whether to provide access, such as the overall volume of requests received or a

³⁹⁴ See e.g., Health Canada, Special access program for drugs : guidance document for industry and practitioners (Revised 2022), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/special-access/drugs/guidance/sap-drugs-guid-ld-eng.pdf>> at p.7.

³⁹⁵ Gibson, Shannon & Trudo Lemmens, “The Promise and Peril of Adapting the Regulatory System to the Pharmacogenomic Context” (2015) 8:2 McGill Journal of Law and Health.

³⁹⁶ Bureau of Policy, Science and International Programs, Special Access Programme Working Group, *Special Access Programme Issue Identification Paper* (Health Canada (Therapeutic Products Directorate), 2007) at p.10.

manufacturer's unwillingness to set up clinical trials in Canada, during the review of an individual request".³⁹⁷

In reality, Health Canada actually does make some effort to encourage market entry of drugs that are widely accessed under the SAP; however, this occurs only on an informal *ad hoc* basis. In response to a query from the author about this largely undocumented practice, Health Canada responded via email as follows: "While the process is informal, Health Canada approaches manufacturers who have supplied drugs through SAP that have the highest number of authorisations, have been on the program on a continuous basis for several years, and in large volumes".³⁹⁸ However, this same email also illustrates how ineffective this approach has been:

In 2016, manufacturers of three of the most request <sic> drugs on the Program filed drug submissions with Health Canada that were approved. In 2017, two other drugs were approved for the Canadian market. In 2018 one drug has been approved for the Canadian market.³⁹⁹

Six drugs over a three-year period is hardly a success story, given the hundreds of drugs requested via the SAP every year. This is particularly the case given the logical assumption that the most widely used drugs would – all else being equal – be more likely to be seen as worth bringing to market from a commercial perspective. The identities of these six drugs were not revealed in the email. Their patent status also remains unknown. Given the timing, it is possible that ivermectin was one of them. If that were the case, however, the fact that Health Canada had been involved in conversations with Merck about bringing ivermectin to market since at least the early 2000s would be further evidence this informal mechanism is

³⁹⁷ Bureau of Policy, Science and International Programs, Special Access Programme Working Group, *Special Access Programme Issue Identification Paper* (Health Canada (Therapeutic Products Directorate), 2007) at p.10.

³⁹⁸ Personal communication, Health Canada Policy Bureau Enquiries, Oct 10, 2018.

³⁹⁹ Personal communication, Health Canada Policy Bureau Enquiries, Oct 10, 2018. The 2018 figure obviously does not extend to last 2.5 months of that year.

not highly effective.⁴⁰⁰ It appears this informal practice has also been in place for a long time; a 1985 article highlights how “the status of the most frequently requested ‘emergency drug’, the antimalarial Fansidar (pyrimethamine and sulfadoxine), may well change in the near future now that the manufacturer, following considerable encouragement from the Bureau of Human Prescription Drugs and the medical community, has presented [...] a submission for the purpose of marketing the product in Canada”.⁴⁰¹ Pyrimethamine/sulfadoxine had been added to the WHO MEML in 1979. Fansidar would ultimately not enter the Canadian market until the last day of 1989; ironically, it would be discontinued in Canada in 2000, though it remains on the WHO MEML. In any event, the evidently longstanding practice of informally encouraging market entry for the most widely used drugs under the SAP does little for patients with less common conditions, regardless of how useful the drug might be or how long it has been in regulatory limbo.

Another aspect of the issue when it comes to old but useful drugs involves what constitutes a “new” drug in Canadian law. In the ordinary sense of the term, decades-old Essential Medicines widely used elsewhere in the world would hardly seem to qualify as “new”. However, the *Food and Drug Regulations* stray from the ordinary to define a “new drug” as follows:

C.08.001 For the purposes of the Act and this Division, *new drug* means a drug, other than a veterinary health product,

- (a) that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug;

⁴⁰⁰ Co-author Brian Ward was directly involved in these (unsuccessful) discussions. Houston, Adam R et al., “Reforming Canada’s Special Access Programme (SAP) to improve access to off-patent essential medicines” (2018) 3:2 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 100–107, online: <<http://jammi.utpjournals.press/doi/10.3138/jammi.2018.01.04>>.

⁴⁰¹ White, G F & MJ Davis, “Antiparasitic drugs: availability and regulatory requirements for ‘emergency’ supply” (1985) 132:3 Can Med Assoc J 273–274.

- (b) that is a combination of two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug; or
- (c) with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration or duration of action, and that has not been sold for that use or condition of use in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug.

Shared across all three categories is the criterion that the substance “has not been sold... *in Canada* for sufficient time and in sufficient quantity to establish *in Canada* safety and effectiveness [*emphasis added*]” of that substance for use as a drug.⁴⁰²

The dual emphasis on Canada – involving both sale in Canada and the establishment of safety and efficacy here – is a particularly awkward fit for those Essential Medicines that have never been formally approved in this country but have been obtained regularly via the SAP for decades and are considered the standard of care under both Canadian and international guidelines.⁴⁰³

Despite barriers to accessing standard of care Essential Medicines, the primary legal challenges regarding the status of drugs under the SAP have stemmed not from patients or physicians, but from drug companies. Unsurprisingly, while much of this litigation has implicated Essential Medicines, unlucrative Neglected Diseases have generally not been the focus of these companies’ efforts; nonetheless, the outcomes have important implications for the drugs at the centre of this thesis. As discussed further below, Canadian courts have consistently held that long-term, widespread access under the SAP does *not* count for regulatory purposes such as establishing safety and efficacy. Unfortunately, however, this does nothing to improve access for Essential Medicines that drug

⁴⁰² The third instance, referring to dosages, routes of administration, and a particular use is where issues like compounding and off-label use may also enter the conversation.

⁴⁰³ As will be seen, “sold” will also prove to be a word capable of differing legal definitions when it comes to the Special Access Programme.

companies show little interest in selling in the first place. In turn, such decisions have also served to showcase cracks in the walls separating the governance of marketed and unmarketed medicines. Officially, however, the tools used to access these unmarketed drugs right now – primarily the SAP – remain almost completely disconnected from the steps necessary to bring them to market. The adoption of a pragmatic approach to the relationship between formal and informal access when it comes to Essential Medicines is overdue.

The SAP as a path to regulatory approval (*Hospira*)

The issue of the intersection of the SAP with formal approval has been raised in the courtroom both by companies whose preferred outcome would be that access via the SAP serve as a form of regulatory approval for their own drug, and those desiring quite the opposite outcome for their competitors. In a series of cases illustrating the former stance, Hospira Healthcare Corporation (“Hospira”) sought regulatory approval for “Drug A”.⁴⁰⁴ In the first of these cases (2008), Hospira challenged a prothonotary’s decision concerning the Minister of Health’s refusal to consider Hospira’s NDS for Drug A; the Minister’s refusal was based on the fact the NDS did not include clinical trial data establishing the safety and efficacy of the drug.⁴⁰⁵ In its argument, Hospira pointed out that Drug A had been supplied through the SAP since 1999 for treatment of the relevant indications. Moreover, because Drug A had come into common use for those indications via the SAP, Hospira argued, it “could not have conducted the usual clinical trials or generated data required by the *Food and Drug Regulations* to establish safety and efficacy without significant ethical concerns”.⁴⁰⁶ In other words, use of Drug A, obtained via the SAP, was already so widespread that it would be impossible to conduct an ethical clinical trial. The plot thickens further, as Hospira alleged that Health

⁴⁰⁴ While not confirmed with absolute certainty, it appears that Drug A is very likely to be the cancer drug oxaliplatin, which figures into much of the jurisprudence around the SAP. Evidence for this assertion, as well as a sequel of sorts to Hospira’s difficulties obtaining an NOC, can be seen some years after the current series of cases, in *Hospira Healthcare Corporation v. Canada (Health)*, 2015 FC 1205. Oxaliplatin was added to the WHO MEML in 2015.

⁴⁰⁵ *Hospira Healthcare Corporation v. Canada (Attorney General)*, 2008 FC 355 (CanLII), <<http://canlii.ca/t/1wf1p>> at para 4.

⁴⁰⁶ *Hospira Healthcare Corporation v. Canada (Attorney General)*, 2008 FC 355 (CanLII), <<http://canlii.ca/t/1wf1p>> at para 5.

Canada had undertaken that it “would define criteria and specifications with respect to the evidence required to establish the safety and efficacy of Drug A that would respect the unique clinical environment of the drug”, only to renege on this commitment.⁴⁰⁷ This intriguing issue of finding means of formally assessing unmarketed drugs already in common use via the SAP was not ultimately explored in this initial court decision, however, as the Federal Court concluded the prothonotary’s decision was not, per the standard of review, clearly wrong.

The same issue was raised again, and again left unresolved, when Hospira subsequently requested judicial review of the decision of the Therapeutic Products Directorate of Health Canada to reject the NDS for Drug A.⁴⁰⁸ In this instance, the Federal Court observed that even though the drug had not been issued an NOC, it had been available in Canada through the SAP. Furthermore, it noted the respondents (the Minister of Health and the Attorney General of Canada) did not dispute that the drug “is widely used in western countries and is now considered a ‘standard of care’ drug” for the intended indication.⁴⁰⁹ Health Canada nevertheless took the position that the applicant would have to file a full NDS, not an Abbreviated NDS (ANDS); in turn, it rejected the NDS for not supplying all the information required by the *Food and Drug Regulations*, including clinical trial data. Here too, the decision indicates it was understood by the parties that the normal clinical trial requirements would be hard to satisfy, and the manner of how to satisfy such requirements came under discussion (though the details of this discussion are once again not provided).⁴¹⁰ Ultimately, however, the Court upheld the rejection as reasonable.

The issue of the role of the SAP was finally tackled head-on in the appeal from this latter decision.⁴¹¹ Here, the Federal Court of Appeal allowed Hospira to

⁴⁰⁷ *Hospira Healthcare Corporation v. Canada (Attorney General)*, 2008 FC 355 (CanLII), <<http://canlii.ca/t/1wf1p>> at paras 6-7.

⁴⁰⁸ *Hospira Healthcare Corporation v. Canada (Attorney General)*, 2010 FC 213 (CanLII), <<http://canlii.ca/t/2939z>>.

⁴⁰⁹ *Hospira Healthcare Corporation v. Canada (Attorney General)*, 2010 FC 213 (CanLII), <<http://canlii.ca/t/2939z>> at para 4.

⁴¹⁰ *Hospira Healthcare Corporation v. Canada (Attorney General)*, 2010 FC 213 (CanLII).

⁴¹¹ *Hospira Healthcare Corporation v. Canada (Attorney General)*, 2010 FCA 345 (CanLII), online: <<https://canlii.ca/t/2939z>>.

succeed on other grounds, but affirmed its acceptance of the Minister's submissions that "the safety and efficacy of a drug cannot be established solely on the basis that its use has been permitted under the Special Access Programme, even if permission has been given thousands of times as is the case with the drug in issue".⁴¹² As yet, the potential leeway left in the decision by the qualification that safety and efficacy cannot be established *solely* on the basis of SAP use does not appear to have been tested; subsequent cases cast a further damper on use of access via the SAP in a regulatory context.

Can a drug widely obtained via the SAP be innovative? (Teva)

Similar reasoning is on display in a series of cases approaching the issue from the opposite perspective. Here, access via the SAP was raised not in an attempt to ease a drug's path to market, but instead to challenge the novelty of a competitor's product. In 2011, Teva Canada ("Teva") attempted to have the Sanofi-Aventis ("Sanofi") cancer drug Eloxatin (Sanofi's trade name for oxaliplatin) removed from Health Canada's Register of Innovative Drugs. Under Canadian law, an "innovative drug" goes beyond being a new drug. Per the *Food and Drug Regulations*, an innovative drug is "a drug that contains a medicinal ingredient not previously approved in a drug by the Minister and that is not a variation of a previously approved medicinal ingredient such as a salt, ester, enantiomer, solvate or polymorph".⁴¹³ Presence on the Register grants additional legal protections to an "innovative drug", in particular an eight-year market exclusivity rooted in data exclusivity.⁴¹⁴ This added protection is unrelated to patent status and corresponds to Canada's trade commitments.⁴¹⁵ In this case, the Minister rejected Teva's initial request to have Eloxatin removed from the Register; Teva challenged that rejection, arguing that by authorizing "Sanofi's wide-scale and high volume sale of [Eloxatin]

⁴¹² *Hospira Healthcare Corporation v. Canada (Attorney General)*, 2010 FCA 345 (CanLII) at para. 6.

⁴¹³ C.08.004.1(1), *Food and Drug Regulations*.

⁴¹⁴ For a discussion of these provisions, see Kendall, Megan & Declan Hamill, "A Decade of Data Protection for Innovative Drugs in Canada: Issues, Limitations, and Time for a Reassessment" (2016) 35:6 Biotechnology Law Report 259–267, online: <<http://www.liebertpub.com/doi/10.1089/blr.2016.29030.mk>>.

⁴¹⁵ In particular, per C.08.004.1(2) of the *Food and Drug Regulations*, it implements of elements of the Canada-United States-Mexico Agreement (CUSMA) trade agreement and of the World Trade Organization Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS).

under the SAP between 1999 and 2005”, the Minister had approved the safety and efficacy of the drug, thus making it ineligible for inclusion on the Register.

The rejection of Teva’s request was initially upheld by the Federal Court.⁴¹⁶ That decision was itself appealed. During the appeal, it was established that the large-scale access to Eloxatin through the SAP amounted to thousands of uses, for which the Minister also received information on adverse effects.⁴¹⁷ Teva submitted that this information amounted to “in effect, a huge clinical trial that yielded more information than what appears in many new drug submissions”.⁴¹⁸ The Federal Court of Appeal disagreed, stating Teva’s position created uncertainty and lack of clarity. For instance, asked the Court, “How many authorizations under the Special Access Programme would be required in order to make a drug ‘approved’ under [...] the *Regulations*?”⁴¹⁹ On the issue of eligibility as an innovative drug, the Court concluded that the “Minister correctly found that Eloxatin met the definition of ‘innovative drug’ and so she was right to keep it on the register of innovative drugs”.⁴²⁰ After all, despite years of use, oxaliplatin had never been approved in Canada; this is precisely why access was dependent on the SAP. Thus, Canadian courts once again emphasized that the SAP is no substitute for formal approval.

To recap both the *Hospira* and *Teva* series of cases: the SAP is not a pathway to market approval for pharmaceuticals. Canadian courts have affirmed that even long-term, widespread access via the SAP is not equivalent to approval, nor is it considered a means sufficient to establish the safety and efficacy of a drug leading to approval. This is the case even where it is acknowledged that the drug constitutes the standard of care. As such, these cases highlight a key problem: Canada seems unable to reconcile its broader recognition of widely used drugs that

⁴¹⁶ *Teva Canada Limited v. Canada (Health)*, 2011 FC 507 (CanLII), online: <<http://canlii.ca/t/flb3n>> at para 3.

⁴¹⁷ *Teva Canada Limited v. Canada (Health)*, 2012 FCA 106 (CanLII), online: <<http://canlii.ca/t/fqx9k>> at para 29.

⁴¹⁸ *Teva Canada Limited v. Canada (Health)*, 2012 FCA 106 (CanLII), online: <<http://canlii.ca/t/fqx9k>> at para 29.

⁴¹⁹ *Teva Canada Limited v. Canada (Health)*, 2012 FCA 106 (CanLII), online: <<http://canlii.ca/t/fqx9k>> at para 32.

⁴²⁰ *Teva Canada Limited v. Canada (Health)*, 2012 FCA 106 (CanLII), online: <<http://canlii.ca/t/fqx9k>> at para. 5.

form the standard of patient care with the very particular manner in which drugs receive formal market approval.

Once again, as a means to prevent a pharmaceutical company from simply bypassing the regulatory process as a matter of expedience in order to sell a new drug as quickly as possible, with insufficient oversight of safety, efficacy and quality, there is logic to the idea of a wall between use via the SAP and formal regulatory approval. In practice, however, this goal is not actually achieved either. A drug company can continue to earn money selling a drug under the SAP, making thousands of sales for years or potentially even decades, without ever formally bringing that drug to market. As the Supreme Court of Canada has noted, in a case coming up on the docket: “There is no limit on the volume of sales that can be made pursuant to the SAP, nor on the period of time that a manufacturer may supply the medicine through it”.⁴²¹ Thus, the drug company can continue to earn money from an unapproved drug in Canada, while saving the expenses associated with having safety, efficacy and quality reviewed as part of the approval process, as well as ongoing costs after approval. The immediate disadvantages of accessing a drug via the SAP, and arranging payment for it if it is not being provided for free, accrue primarily to the patient and their physician, not the pharmaceutical company.

Thalidomide: A notorious regulatory failure turned Essential Medicine

Further incongruities of the pharmaceutical regulatory system are demonstrated in circumstances where a drug currently accessible only via the SAP had previously been approved in Canada, before being withdrawn from the market. Drugs such as pyrimethamine and cycloserine, discontinued for commercial reasons despite remaining important for patient care, are a grey area when it comes to “new drugs” under the *Food and Drug Act*. In the absence of alternative pathways for access, however, the SAP remains in practice the primary mechanism to access “drugs that had a market authorization in Canada at one time and were discontinued from the market”.⁴²² The most prominent court case in this regard involves a drug that

⁴²¹ *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 (CanLII), [2011] 1 SCR 3 at para. 4.

⁴²² Health Canada, Special access program for drugs : guidance document for industry and practitioners (Revised 2022), online: <<https://www.canada.ca/content/dam/hc->

comparatively few know is used to treat a Neglected Disease, despite being perhaps the most notorious, and most influential, drug in the history of pharmaceutical regulation: Thalidomide. This drug would drive the creation of the modern pharmaceutical regulatory system not just in Canada but in many countries around the world; in doing so, it would also indirectly lead to the creation of the SAP itself. Its return to the Canadian market would raise further questions about access to useful drugs via the SAP.

Thalidomide was developed in the late 1950s in Europe as a sedative, but soon became popular as a treatment for morning sickness.⁴²³ It was first approved for sale in Canada, made by two different companies, in 1961.⁴²⁴ Thalidomide was widely used in many countries; however, it was soon discovered to be teratogenic (harmful to the fetus).⁴²⁵ By March 1962, the two licensed companies had withdrawn it from the Canadian market, although the drug itself had also widely circulated via the distribution of samples to physicians.⁴²⁶ The *Food and Drugs Act* was amended that year to prohibit, by name, the sale of thalidomide.⁴²⁷ However, by this time numerous pregnancies had already been affected, with many failing to result in a live birth, and others in children born with serious physical defects; it was, as described at the time, the “first recorded epidemic of iatrogenic disease affecting the human fetus”.⁴²⁸ The thalidomide experience marked a turning point

sc/documents/services/drugs-health-products/special-access/drugs/guidance/sap-drugs-guid-ld-eng.pdf > at p.14.

⁴²³ Rehman, Waqas, Lisa M Arfons & Hillard M Lazarus, “The rise, fall and subsequent triumph of thalidomide: lessons learned in drug development” (2011) 2:5 *Ther Adv Hematol* 291–308.

⁴²⁴ Webb, J F, “Canadian Thalidomide Experience” (1963) 89 *Can Med Assoc J* 987–992. It was marketed as Kevadon by the American company Richardson-Merrell, and Talimol by the Montréal-based Frank W. Horner.

⁴²⁵ Vargesson, Neil, “Thalidomide-induced teratogenesis: history and mechanisms” (2015) 105:2 *Birth Defects Res C Embryo Today* 140–156.

⁴²⁶ Herder, M et al., “Regulating prescription drugs for patient safety: Does Bill C-17 go far enough?” (2014) 186:8 *Canadian Medical Association Journal* E287–E292, online:

<<http://www.cmaj.ca/cgi/doi/10.1503/cmaj.131850>>; see also *An Act to Amend the Food and Drugs Act*, S.C. 1962, c. 15.

⁴²⁷ *An Act to Amend the Food and Drugs Act*, S.C. 1962, c. 15. In a very 1960s twist, the new schedule of banned drugs (Schedule H), at the time of its creation, consisted of two drugs: thalidomide and lysergic acid diethylamide (LSD).

⁴²⁸ Webb, J F, “Canadian Thalidomide Experience” (1963) 89 *Can Med Assoc J* 987–992.

in Canadian drug regulation, as it did elsewhere in the world.⁴²⁹ Compensation for the victims of the disaster, tragically, was not so rapid, at least in Canada; the most recent class-action settlement for victims was only approved in 2020.⁴³⁰

All of this illustrates the notoriety of thalidomide, especially when it comes to effectively regulating drug safety. At the same time, as countries reacted by bringing in more stringent requirements for ensuring safety and efficacy, an unintended regulatory side-effect was that companies were unwilling to undergo the added time and expense of approval for drugs for conditions unlikely to turn large profits, including both Rare Diseases and Neglected Diseases.⁴³¹ By extension, the reforms brought about in Canada by thalidomide would also lead to the regulations underpinning the SAP in 1966.⁴³² As the regulatory process became more stringent, a mechanism was needed to ensure interim access for drugs awaiting approval; ultimately, this would prove to be an essentially permanent pathway for accessing drugs not considered worth bringing to the Canadian market at all.

Despite its fame as the archetypal example of pharmaceutical regulatory failure, thalidomide is also an important and versatile drug for a range of conditions. This includes Neglected Diseases; it has been used as a treatment for leprosy for over half a century.⁴³³ Indeed, it was being accessed in Canada outside the formal approval process for this purpose by the mid-1980s, if not earlier.⁴³⁴ However, it would primarily be as a cancer treatment that it would return to the public eye in Canada (it is also as a cancer treatment that it would be added to the

⁴²⁹ See e.g., Greene, Jeremy A & Scott H Podolsky, "Reform, regulation, and pharmaceuticals--the Kefauver-Harris Amendments at 50" (2012) 367:16 N Engl J Med 1481–1483; Krapohl, Sebastian, "Thalidomide, BSE and the single market: An historical-institutionalist approach to regulatory regimes in the European Union" (2007) 46:1 Eur J Political Res 25–46, online: <<http://doi.wiley.com/10.1111/j.1475-6765.2006.00643.x>>.

⁴³⁰ *Wenham v. Canada (Attorney General)*, 2020 FC 588.

⁴³¹ See e.g., Shirkey, H, "Therapeutic orphans" (1968) 72:1 J Pediatr 119–120.

⁴³² "Food and Drug Regulations, amended", *Canada Gazette, Part II*, Vol.100, no. 22, (23 November 1966) p. 517–518.

⁴³³ See e.g., Iyer, C G et al., "WHO co-ordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients" (1971) 45:6 Bull World Health Organ 719–732.

⁴³⁴ White, G.F. & M.J. Davis, "Antiparasitic drugs: availability and regulatory requirements for 'emergency' supply" (1985) 132:3 Can Med Assoc J 273–274.

WHO MEML in 2019).⁴³⁵ Bringing a drug as infamous as thalidomide – even repurposed for a totally different condition – back to Canada was always going to raise eyebrows.⁴³⁶ Its return to the formal market would also be a source of litigation that would in turn implicate the SAP.

By 1995, thalidomide – now rebranded as Thalomid – was being accessed regularly via the SAP from the pharmaceutical company Celgene for treatment of leprosy and conditions associated with HIV; it was also being widely accessed for treatment of certain cancers.⁴³⁷ The access problems it faced under the SAP are much like those already described for other drugs. During the years that it could be obtained only via the SAP, even as it was recommended as standard therapy by multiple Canadian healthcare bodies, delays were common. According to care providers responding to one 2010 survey on cancer treatment “54% (66/122) indicated an average delay of 1 month, and 34% (41/122), an average delay of 2 months”.⁴³⁸ Further concerns included the fact that Health Canada only permitted SAP access to the more expensive Celgene-produced version, rather than cheaper generic versions produced elsewhere, despite the fact no version of the drug was officially approved in Canada.⁴³⁹ Minuk and colleagues conclude: “Clearly, the sap <sic> is not designed for the standard day-to-day treatment of diseases such as myeloma, in which thalidomide is considered ‘conventional therapy’”.⁴⁴⁰ This reflects how the inadequacies of the SAP are not restricted to Neglected Diseases (even if the very same drug might be used to treat them). These access barriers were further magnified by the volume of thalidomide used in Canada. As the

⁴³⁵ It is indicated on the WHO MEML for plasma cell myeloma.

⁴³⁶ See e.g., Mackenzie, Robert, “Thalidomide was a disaster. And it’s available in Canada again.” *Maclean’s* (30 March 2017), online: <<https://www.macleans.ca/society/health/thalidomide-was-a-disaster-and-its-available-in-canada-again/>>.

⁴³⁷ *Celgene Inc. v. Canada (Health)*, 2012 FC 154 (CanLII), <<http://canlii.ca/t/fq1fm>> at para 11.

⁴³⁸ Minuk, L et al. “Access to thalidomide for the treatment of multiple myeloma in Canada: physician behaviours and ethical implications” (2010) 17:4 *Curr Oncol* 11–19.

⁴³⁹ Minuk, L et al. “Access to thalidomide for the treatment of multiple myeloma in Canada: physician behaviours and ethical implications” (2010) 17:4 *Curr Oncol* 11–19. As a sidenote, attempts to request a cheaper version from Mexico via the SAP are raised in one Worker’s Compensation Tribunal case in British Columbia; while the Tribunal rules in favour of covering this unapproved treatment, no clear answer is provided as to the ultimate source it is to be obtained from. *WCAT-2004-05200 (Re)*, 2004 CanLII 87080 (BC WCAT), online: <<https://canlii.ca/t/g3nkc>>.

⁴⁴⁰ Minuk, L et al. “Access to thalidomide for the treatment of multiple myeloma in Canada: physician behaviours and ethical implications” (2010) 17:4 *Curr Oncol* 11–19.

Supreme Court of Canada would soon hear, “of the approximately 26,000 requests made under the SAP in 2006 by medical practitioners, approximately 4,500 were for thalidomide, making it the most frequently sourced drug under the SAP”.⁴⁴¹ In fact, court proceedings would reveal that thalidomide is one of that small number of drugs for which the high number of SAP requests has led Health Canada to successfully, albeit informally, lobby the manufacturer to bring the drug to market.⁴⁴²

At the centre of the initial series of proceedings around thalidomide was its legal status in Canada. This contrasted with its status south of the border. In a reversal of the usual approval pattern, thalidomide had not been approved in the United States in the 1960s. This was not a matter of market size, however, but of safety concerns raised by a Canadian employee of the US FDA, Dr. Frances Kelsey.⁴⁴³ Although the US thus avoided the thalidomide tragedy, the drug still proved the tipping point for the regulatory reforms of the well-known Kefauver-Harris Amendments, which required evidence of efficacy as well as safety in the United States.⁴⁴⁴ At the same time, the consequence of never having been approved was that thalidomide was a “new” drug for legal purposes in the US when it was ultimately brought to market for other conditions. In that country, its first formal approval, in 1998, would actually be as an Orphan Drug for a Neglected Disease: leprosy.⁴⁴⁵ As in Canada, it was also widely used off-label for conditions associated

⁴⁴¹ *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 (CanLII), [2011] 1 SCR 3 at para. 5.

⁴⁴² *Celgene Inc. v. Canada (Health)*, 2012 FC 154 (CanLII), <<http://canlii.ca/t/fq1fm>> at para 11. It is not clear how influential Health Canada was.

⁴⁴³ It's not a Nobel Prize, but Dr. Kelsey won numerous awards for her work; indeed, part of this thesis was written down the street from Frances Kelsey Secondary School in Mill Bay, British Columbia. See also Kelsey, Frances O, “Thalidomide update: regulatory aspects” (1988) 38:3 *Teratology* 221–226.

⁴⁴⁴ Although, as some have pointed out, these changes were actually a notably watered-down version of the original proposal. See e.g., Greene, Jeremy A & Scott H Podolsky, “Reform, regulation, and pharmaceuticals--the Kefauver-Harris Amendments at 50” (2012) 367:16 *N Engl J Med* 1481–1483.

⁴⁴⁵ Orphan Drugs will be revisited later in this thesis. Rajkumar, S Vincent, “Thalidomide: Tragic Past and Promising Future” (2004) 79:7 *Mayo Clinic Proceedings* 899–903, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0025619611621575>>.

with HIV.⁴⁴⁶ However, as elsewhere, thalidomide would most commonly be used as a cancer drug.

In turn, while it has never been formally approved for leprosy treatment in Canada, thalidomide would ultimately receive Health Canada approval for certain forms of cancer; it was first formally marketed for this purpose in 2010.⁴⁴⁷ The legal path to get there, however, was notably more complex than in the US, involving the murkier story of a drug once approved, then banned by name, then brought back decades later for a completely different set of indications. After many years of access via the SAP, the pharmaceutical company Celgene finally filed an NDS, which was granted. A dispute arose, however, after the drug was refused a place on the Register of Innovative Drugs, a decision Celgene challenged in court. Thalidomide's unique regulatory history came into play in what followed. After all, thalidomide had not merely been removed from the market in Canada but obliterated from it. As the Federal Court of Appeal would describe the situation later in this chain of proceedings:

Parliament's many legislative responses over the years also demonstrate the unique situation presented by thalidomide. It was the only medicinal ingredient to ever be expressly prohibited alongside various illegal street drugs; it, at times, received its very own sections and schedules within the [Food and Drugs] Act; and it persisted within the Act even after dramatic overhauls further modified the administration of restricted substances—relegating those street drugs that were previously considered alongside it to other pieces of legislation.⁴⁴⁸

⁴⁴⁶ See e.g., "Thalidomide approved" (1998) 9:5 Posit Aware 16.

⁴⁴⁷ In turn, because it is now formally approved in Canada, off-label use for leprosy becomes easier.

⁴⁴⁸ *Canada (Health) v. Celgene Inc.*, 2013 FCA 43 (CanLII) at para 75.

At the initial trial, the Federal Court quashed the Minister's decision, and added Thalomid to the Register of Innovative Drugs.⁴⁴⁹ In doing so, the judge states that "the fact of the matter is that thalidomide was determined to be unsafe and returned to the status of a new drug"; the fact it could no longer be used as a reference for an ANDS is also noted.⁴⁵⁰ Interestingly, however, in addressing the question of the Minister's original approval of the drug, the judge also suggests that the general rule that ministerial approval "need not have been made under the current version of that provision" under the *Food and Drugs Act* might not apply in a situation where the scheme in question had been "substantively and significantly" modified.⁴⁵¹ There is no question that the scheme had been "substantively and significantly modified" in this instance. Thalidomide had been approved pursuant to the 1955 version of the regulatory scheme; the drastic revision of 1963 was precipitated by thalidomide itself.⁴⁵² As observed by the Federal Court, it was this very revision that introduced current requirements into the *Food and Drugs Act*.⁴⁵³ Thus, it is an understatement to say thalidomide found itself in unique circumstances.

On appeal, the Federal Court of Appeal restored Thalomid's initial rejection from the Register. It did so by interpreting inclusion on the Register in terms of a novel medicinal ingredient; by taking this approach, the Court found the novelty of the medicinal ingredient itself, not its indication, to be the deciding factor.⁴⁵⁴ The dissent strongly disagrees, supporting the conclusion of the trial judge. Drawing from the *Teva* cases discussed earlier, the dissent asserts that "the drugs being accessed through the [Special Access] programme cannot be considered to be approved for use in Canada" and that in turn it "follows that since thalidomide was

⁴⁴⁹ *Celgene Inc. v. Canada (Health)*, 2012 FC 154 (CanLII), online: <<http://canlii.ca/t/fq1fm>>.

⁴⁵⁰ *Celgene Inc. v. Canada (Health)*, 2012 FC 154 (CanLII), online: <<http://canlii.ca/t/fq1fm>> at para 41.

⁴⁵¹ *Celgene Inc. v. Canada (Health)*, 2012 FC 154 (CanLII), online: <<http://canlii.ca/t/fq1fm>> at paras 45-46.

⁴⁵² *Celgene Inc. v. Canada (Health)*, 2012 FC 154 (CanLII), online: <<http://canlii.ca/t/fq1fm>> at para 44.

⁴⁵³ *Celgene Inc. v. Canada (Health)*, 2012 FC 154 (CanLII), online: <<http://canlii.ca/t/fq1fm>> at para 46.

⁴⁵⁴ *Canada (Health) v. Celgene Inc.*, 2013 FCA 43 (CanLII), online: <<https://canlii.ca/t/fw4zb>>.

being accessed through the SAP, it was not approved for use in Canada”.⁴⁵⁵

Nevertheless, the use of the SAP is not ultimately determinative in the dissent; it goes on to argue that the “Patented Medicine (Notice of Compliance) regime demarcates separate roles for innovative and generic drugs” and therefore, since “thalidomide was not on the Canadian market prior to its reintroduction by Celgene, and therefore not available to serve as a reference product for a generic manufacturer, it follows that the more appropriate space for thalidomide to occupy is that of an innovative drug”.⁴⁵⁶ This seems unconvincing; following this line of reasoning would raise questions about the status of a drug voluntarily withdrawn from the market, and potentially even how such voluntary withdrawal could be exploited for commercial advantage by subsequently returning the withdrawn drug to market as an innovative drug in the absence of a marketed reference product.⁴⁵⁷

While the dissent’s argument fails to convince on its central points, it nevertheless highlights some of the barriers old medicines face entering the Canadian market. For instance, having to file an NDS rather than an abbreviated ANDS in the absence of a current reference product does make the process more complex. For an old drug viewed to have very limited financial potential, having to file a full NDS is itself a disincentive. This applies to market re-entry as well, and is not limited to a drug once explicitly banned by Act of Parliament. That said, there is some limited scope to address the issue of previously marketed drugs returning to the market within the existing regulatory framework; for instance, Health Canada

⁴⁵⁵ *Canada (Health) v. Celgene Inc.*, 2013 FCA 43 (CanLII), online: <<https://canlii.ca/t/fw4zb>> at para 82. This is a somewhat misleadingly phrased point; for instance, in some circumstances an unapproved version of an approved drug may be obtained via the SAP, including in some cases of shortage. See e.g., Multi-Stakeholder Steering Committee on Drug Shortages in Canada, *Multi-Stakeholder Toolkit - A Toolkit for Improved Understanding and Transparency of Drug Shortage Response in Canada*, by Multi-Stakeholder Steering Committee on Drug Shortages in Canada (2017), online: <https://www.drugshortagescanada.ca/files/MSSC_Toolkit_2017.pdf> at p.14.

⁴⁵⁶ *Canada (Health) v. Celgene Inc.*, 2013 FCA 43 (CanLII), online: <<https://canlii.ca/t/fw4zb>> at para 71.

⁴⁵⁷ A similar argument was raised in the proceedings about “opening the floodgates to any number of other drug companies that would try to attain data protection for drugs with an inconsistent Canadian approval history”, something the dissent unconvincingly dismisses by stating “this decision is necessarily narrow in scope and does not generate these slippery slope concerns”. With respect, while thalidomide is indeed a unique story, this opinion does not sufficiently differentiate its circumstances from those of other discontinued drugs. *Canada (Health) v. Celgene Inc.*, 2013 FCA 43 (CanLII), online: <<https://canlii.ca/t/fw4zb>> at paras 100-101.

does have a process to apply to reinstate a DIN.⁴⁵⁸ Current guidance indicates that, at the discretion of Health Canada, “DIN(s) may be reissued without the filing of a submission and at no cost, if the manufacturer can attest that there has been no change to the drug or its label since the cancellation of the DIN”.⁴⁵⁹ This means that in some instances, such as where the same company that withdrew the drug in Canada still manufactures the same product for other markets (as with GlaxoSmithKline and pyrimethamine), this could potentially be a relatively simple path to re-entry; unfortunately, having a smooth path to re-entry does not itself resolve the underlying reasons for departing the market in the first place. Meanwhile, for new market entrants looking to fill a niche for an old discontinued drug, the path is less straightforward, even if perhaps not closed entirely; the *Food & Drug Regulations* do provide that a Canadian Reference Product underpinning an ANDS may include a “drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug in respect of which a notice of compliance has been issued under section C.08.004 or C.08.004.01 cannot be used for that purpose because it is no longer marketed in Canada”.⁴⁶⁰ Thus, there is at least the possibility that a previously discontinued drug returning to the market might not have to be treated as completely novel. However, if this approach has ever been attempted for a once-marketed Essential Medicine for a Neglected Disease, this author has found no record of it.

Taking steps to promote this approach to a wider range of prospective market entrants – including existing international producers already meeting

⁴⁵⁸ Health Canada, Guidance document: regulatory requirements for drug identification numbers (DINs) (May 2019), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/regulatory-requirements-drug-identification-numbers/document/regulatory-requirements-drug-identification-numbers-guidance.pdf>> Appendix A “Template email - Request for DIN reissuance”.

⁴⁵⁹ Health Canada, Guidance document: regulatory requirements for drug identification numbers (DINs) (May 2019), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/regulatory-requirements-drug-identification-numbers/document/regulatory-requirements-drug-identification-numbers-guidance.pdf>> at p.24.

⁴⁶⁰ *Food & Drug Regulations* C.08.001.1(b).

appropriate foreign regulatory standards – could potentially have some utility for previously approved but discontinued drugs like cycloserine and pyrimethamine. At the same time, this would only address at best a subset of drugs missing from the Canadian market, and would do so without resolving many of the broader underlying questions around regulatory goals and access to unmarketed Essential Medicines already established as the standard of care. In any case, this was not the path taken for thalidomide; subsequently, another case involving thalidomide and the SAP would shed light on a very different, but also very relevant, legal issue.

Are drugs obtained via the SAP “sold” in Canada? (*Celgene*)

The Patented Medicine Prices Review Board (PMPRB) has already been raised in this thesis. It is Canada’s primary tool for tackling high drug prices. It is established under the *Patent Act* and has a range of powers to tackle “excessive prices”.⁴⁶¹ And in 2011, the Supreme Court of Canada confirmed that the PMPRB *does* have jurisdiction over patented medicines obtained via the SAP.⁴⁶² It did so in the case that also yielded the observation, remarked upon earlier, that thalidomide was at one point the single drug most accessed via the SAP. Ironically, after years of distribution via the SAP, Thalomid only fell under the PMPRB’s jurisdiction after a Canadian patent was granted in 2006 (the underlying drug, thalidomide, had of course been off patent for decades).⁴⁶³ This decision sits uncomfortably against how Canadian courts, both before (*Hospira*) and after (*Teva*) this case, have separated the realities of clinical use of standard of care drugs in Canada from the fact those drugs were obtained via the SAP. By contrast, in this case the SCC would alter other seemingly basic legal principles to accommodate a different set of public policy objectives around access to medicines via the SAP.

⁴⁶¹ The PMPRB is established under s.83, *Patent Act* (R.S.C., 1985, c. P-4).

⁴⁶² *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 (CanLII), online: <<https://canlii.ca/t/2fbv3>>. This was not a completely novel stance. For instance, the jurisdiction of the PMPRB over patented drugs obtained via the EDRP has been asserted twenty years before. Clark, Edie & Canadian Coordinating Office for Health Technology Assessment, *A Survey of investigational new drug and emergency drug release policies* (Ottawa, Ont.: Canadian Coordinating Office for Health Technology Assessment, 1991) at p.23.

⁴⁶³ *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 (CanLII), online: <<https://canlii.ca/t/2fbv3>> at para. 7.

Under the *Patent Act*, a patentee is required to provide information and documents as specified in the *Regulations* regarding “the price at which the medicine is being or has been sold in any market in Canada” to the PMPRB.⁴⁶⁴ At issue was whether Celgene was obliged to provide such information to the PMPRB for Thalomid sold via the SAP. This raised the question of whether the concept of a medicine being “sold in any market in Canada” should be assessed under traditional commercial law principles, or within the legislative context and mandate of the PMPRB.⁴⁶⁵ This question arose because Thalomid accessed via the SAP came from Celgene’s headquarters in New Jersey, which is also where payment for the drug, in U.S. dollars, was sent.

The Federal Court adopted a standard commercial law interpretation, determining the sale took place in the United States and rejecting PMPRB jurisdiction.⁴⁶⁶ The Federal Court of Appeal found this decision did not properly account for statutory context, and restored the Board’s jurisdiction.⁴⁶⁷ The SCC notes the parties agreed that, under commercial law terms, New Jersey would be considered the locus of the sale.⁴⁶⁸ Crucially, however, the PMPRB’s position – one ultimately accepted by the SCC – was that this definition would not fit its mandate of protecting Canadian consumers from excessive prices for patented drugs. Furthermore, a traditional commercial law interpretation would also have the

⁴⁶⁴ *Patent Act* (R.S.C., 1985, c. P-4), s.80(1)(b).

⁴⁶⁵ *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 (CanLII), online: <<https://canlii.ca/t/2fbv3>> at para. 1.

⁴⁶⁶ *Celgene Corporation v. Canada (Attorney General)*, 2009 FC 271 (CanLII), online: <<https://canlii.ca/t/23trk>>. It is worth noting, however, that the judge also finds previous cases on the jurisdiction of the PMPRB “not directly relevant because they do not involve the sales of medicine outside of Canada” (at para 21). Strictly speaking, this is true; however, it should also be noted that among those discarded precedents, in the very first series of cases to touch on PMPRB jurisdiction, the Federal Court of Appeal had rejected the application of narrow regulatory definitions found in the *NOC Regulations* under the *Patent Act* to the SAP (then the EDRP) on the grounds that “Such a restrictive interpretation would remove from the Board’s jurisdiction products placed on the market via the EDRP process”. Jurisdiction over the EDRP/SAP thus established would in turn logically implicate access to foreign sources. *ICN Pharmaceuticals, Inc. v. Canada (Staff of the Patented Medicine Prices Review Board)*, 1996 1 FC 32 (CanLII 4089), online: <<https://canlii.ca/t/4nbd>>.

⁴⁶⁷ *Canada (Attorney General) v. Celgene Corporation*, 2009 FCA 378 (CanLII), online: <<https://canlii.ca/t/275hg>>.

⁴⁶⁸ *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 (CanLII), online: <<https://canlii.ca/t/2fbv3>> at para. 10.

incongruous effect of giving the PMPRB jurisdiction over drugs sold in Canada but destined for foreign consumers.⁴⁶⁹ Ultimately, the SCC agreed that the PMPRB's mandate should prevail over the normal commercial law interpretation. As such, access to medicines through the SAP was interpreted in a manner that reflected the interest the Canadian consumer has in access to patented medicines that are not excessively priced, whether or not they are formally marketed in Canada.⁴⁷⁰

As a consequence, this decision sets up the unusual situation where drugs accessed under the SAP are affected by two diverging concepts of “sold”, with differing impacts on patient access. Here, the SCC determined that thalidomide obtained via the SAP was “sold in any market in Canada” for the purposes of the *Patent Act*.⁴⁷¹ At the same time, as will be recalled from earlier in this section, the regulatory definition of a new drug under the *Food and Drug Regulations* is one that “has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug”.⁴⁷² The result is that a patented medicine obtained via the SAP could end up as a veritable Schrödinger's Drug, both sold in large quantities in Canada for well over a decade for the purposes of the *Patent Act* and simultaneously not sold in Canada for the purposes of the *Food and Drug Regulations*, depending which legislative regime is being followed. It is difficult to reconcile how these pieces fit together, without again acknowledging that long-term use of a drug under the SAP must mean *something*.⁴⁷³

⁴⁶⁹ *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 (CanLII), online: <<https://canlii.ca/t/2fbv3>> at para. 31.

⁴⁷⁰ It should be noted that since then, the Federal Court of Appeal has narrowed the scope of the SAP in relation to consumer protection. In the 2021 *Alexion* case, the FCA states that “Over and over again, authorities have stressed that the excessive pricing provisions in the *Patent Act* are directed at controlling patent abuse, not reasonable pricing, price-regulation or consumer protection at large”, and that while “In one authority, the Supreme Court loosely and occasionally speaks of these provisions having a consumer protection purpose and cites some politicians’ speeches to that effect” it also “ties that purpose to the specific need to prevent patent abuse”. *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)*, 2021 FCA 157, at para. 49.

⁴⁷¹ *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 (CanLII), online: <<https://canlii.ca/t/2fbv3>> at para. 5.

⁴⁷² C.08.001 *Food and Drug Regulations*.

⁴⁷³ This issue is also touched upon – unfortunately without reference to any of these existing sources of law – in a decision of the Trade-marks Opposition Board, in which the presiding Member of the Board states, “in passing that, in my view” the distribution of an unapproved pharmaceutical

Chapter 5: What is the SAP for?

The Decision-Making Process – HIV and Implants

Long-term recourse to the SAP for standard of care drugs in the absence of any real prospect of formal approval has raised deeper questions not only about the functionality of the SAP, but its underlying purposes. One longstanding concern many physicians have raised regarding the SAP has been with the decision-making process that surrounds each request. As will be seen, however, such questions about the SAP decision-making process serve to raise broader questions around the underlying goals of the pharmaceutical regulatory regime encompassing the SAP, and indeed the regulation of health products in general. According to the SAP itself:

The regulatory authority supporting the SAP is discretionary and a decision to authorize or deny a request is made on a case-by-case basis by taking into consideration the nature of the medical emergency, the availability of marketed alternatives and the information provided in support of the request regarding the use, safety and efficacy of the drug.⁴⁷⁴

While physicians are not infallible in their own decision making, there are real questions about whether discretionary SAP decisions are being made by individuals sufficiently qualified to do so.⁴⁷⁵ Health Canada itself acknowledged

product via the SAP “may be considered use in the normal course of trade for the pharmaceutical industry” even if it “cannot legally be ‘sold’ until it has regulatory approval”. *Ferring, Inc v. Apotex Technologies, Inc*, 2013 TMOB 225 (CanLII) at para. 88.

⁴⁷⁴ Health Canada, Special access program for drugs : guidance document for industry and practitioners (Revised 2022), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/special-access/drugs/guidance/sap-drugs-guid-ld-eng.pdf>> (2020) at p.7.

⁴⁷⁵ Colleagues have informed the author of multiple requests made to the SAP to provide information about the qualifications of SAP decision makers. However, as of this writing, such requests have yet to bear fruit.

over a decade ago that “the lack of clinical expertise within the SAP has led to questions regarding the authority of the SAP to question a practitioner’s medical expertise or to deny access to drugs”.⁴⁷⁶ Unfortunately, this situation has not been resolved in the interim. Recent guidance documents indicate that the SAP “may” consult with expert reviewers within Health Canada, or with Canadian and/or international experts; however, it’s unclear how often this occurs or under what circumstances.⁴⁷⁷ While there are a number of steps that could be taken to address the SAP decision-making process, requiring that standardized references, including the WHO MEML and Canadian treatment guidelines, play an explicit role in the process might help rectify some of these concerns.⁴⁷⁸

Discretionary decision-making by the SAP has led to some controversial outcomes, which in turn have raised further questions about the SAP itself. In a high-profile instance in the early 2000s, a group of physicians were treating six HIV patients for whom “all conventional antiretroviral therapies had failed”.⁴⁷⁹ They applied to use TMC114 and TMC125, two investigational drugs that separately offered limited but promising data, as combination therapy. The request was denied, on the grounds there was lack of sufficient evidence of the use of these products in combination. The unsuccessful applicants, who include some of Canada’s most prominent HIV experts, published a scathing rebuke, questioning

⁴⁷⁶ Bureau of Policy, Science and International Programs, Special Access Programme Working Group, *Special Access Programme Issue Identification Paper* (Health Canada (Therapeutic Products Directorate), 2007) at p.13.

⁴⁷⁷ Health Canada, Special access program for drugs : guidance document for industry and practitioners (Revised 2022), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/special-access/drugs/guidance/sap-drugs-guid-ld-eng.pdf>> at p.21.

⁴⁷⁸ As an aside: Although this thesis has not focused on the procedural fairness aspects of the SAP, it is worth acknowledging a renewed focus on the value of reasons in the context of judicial review in the wake of *Canada (Minister of Citizenship and Immigration) v. Vavilov*, 2019 SCC 65 (at paras.76-81, which also calls back *Baker v. Canada (Minister of Citizenship and Immigration)*, 1999 CanLII 699 (SCC), [1999] 2 SCR 817, and the conclusion that procedural fairness will sometimes require a written decision and reasons, particularly where the decision has important significance for the individual (at para 43.). Although the patient is one step removed from the decision, which implicates the physician, the significance of receiving or not receiving a treatment for a serious or life-threatening emergency seems obvious. This would seem to leave the SAP decision-making process more open to challenge, particularly where written reasons are not provided.

⁴⁷⁹ Christie, Timothy K S, Marianne Harris & Julio S G Montaner. “Special Access Denied: A Case Study of Health Canada’s Special Access Program” (2006) 2:2 *Healthc Policy* 27–34.

the underlying approach taken by the SAP and accusing it, among other things, of using its discretionary authority arbitrarily, and rendering “value-laden decisions camouflaged in the language of evidence-based decision-making”.⁴⁸⁰ In this instance, after a flurry of publicity, Health Canada ultimately offered to make the drugs available, but as part of a clinical trial; by this time, one of the intended patients had died, and one of the applicant physicians described the clinical trial as the “special access program <sic> in all but name”.⁴⁸¹

It must be emphasized that this incident involved experimental medicines, being used in an experimental combination. Today, both of the investigational agents in question, darunavir (TMC114) and etravirine (TMC125), are approved in Canada for the treatment of HIV; darunavir has been added to the WHO MEML. These two drugs are also used in combination with each other.⁴⁸² However, none of this was established at the time, even if treatment would have been under the stewardship of leading experts in the disease in question. This is in contrast to the scenario of specialist physicians requesting established Essential Medicines that are included in treatment guidelines as the standard of care, as in examples presented earlier regarding tuberculosis and parasitic infections.

At the same time, this high-profile incident does serve to raise further concerns about where the SAP fits within the context of the broader goals of the regulation of health products in Canada. Some of the physicians involved, evidently still incensed, highlighted some of these concerns in a subsequent article, pointedly titled “The perverted irony of Health Canada's Special Access Programme”, in which they compare the denial of their request for HIV treatment to the high success rate of Special Access Programme requests for silicone breast implants.⁴⁸³

⁴⁸⁰ Christie, Timothy K S, Marianne Harris & Julio S G Montaner. “Special Access Denied: A Case Study of Health Canada’s Special Access Program” (2006) 2:2 *Healthc Policy* 27–34.

⁴⁸¹ Woodward, Jonathan, “B.C. patients win AIDS drugs trial”, *The Globe & Mail* (21 December 2005), online: <<https://www.theglobeandmail.com/news/national/bc-patients-win-aids-drugs-trial/article4122816/>>.

⁴⁸² For instance, alongside a third drug, ritonavir. See e.g., Cressey, Tim R et al., “Pharmacokinetics of Darunavir/Ritonavir With Etravirine Both Twice Daily in Human Immunodeficiency Virus-Infected Adolescents and Young Adults: Table 1.” (2016) *J Ped Infect Dis* piiw017, online: <<https://academic.oup.com/jpids/article-lookup/doi/10.1093/jpids/piw017>>.

⁴⁸³ Christie, Timothy K S & Julio S G Montaner. “The perverted irony of Health Canada’s Special Access Programme” (2006) 174:12 *CMAJ* 1746.

Their piece draws upon a media investigation which found that over 21,000 Special Access Programme requests for access to silicone breast implants had been approved in the preceding five years.⁴⁸⁴ Per that media report, the conditions used to justify successful requests were “small breasts” and “slight rippling of the skin through saline implants”.⁴⁸⁵ According to another news story, in some years Health Canada approved thousands of requests for such implants while declining none.⁴⁸⁶ This high acceptance rate for a huge volume of implants came despite the fact that Health Canada had placed a moratorium on the use of silicone breast implants in January 1992, in response to concerns about their safety; indeed, these safety concerns had been the subject of litigation.⁴⁸⁷

The contrast between HIV and “slight rippling of the skin” is an immediately striking one. However, it must be noted that the authors – eminent medical, rather than legal, experts – are conflating two different Special Access Programme regulatory regimes. In Canada, breast implants are classified not as a drug, but a medical device.⁴⁸⁸ Special Access to unapproved medical devices comes via a pathway of the same name, but governed by a different set of regulations under the *Food and Drugs Act*. Per the *Medical Device Regulations*, “special access means access to a medical device for emergency use or if conventional therapies have

⁴⁸⁴ “Loophole allows banned silicone implants”, *Global National* (16 February 2006), online (archived copy): <https://web.archive.org/web/20061110040545/http://www.canada.com/globaltv/national/story.html?id=f4ba541d-bd2e-4302-81dd-623b8cffb33f>.

⁴⁸⁵ “Loophole allows banned silicone implants”, *Global National* (16 February 2006), online (archived copy): <https://web.archive.org/web/20061110040545/http://www.canada.com/globaltv/national/story.html?id=f4ba541d-bd2e-4302-81dd-623b8cffb33f>.

⁴⁸⁶ Gandhi, Unnati, “Health Canada approves use of silicone-gel breast implants”, *The Globe & Mail* (21 October 2006), online: <https://www.theglobeandmail.com/news/national/health-canada-approves-use-of-silicone-gel-breast-implants/article654247/>.

⁴⁸⁷ The saga of silicone breast implant litigation is beyond the scope of this thesis, but see e.g., *Bendall v. McGhan Medical Corp.*, 1993 CanLII 5550 (ON SC), online: <https://canlii.ca/t/1wc12>. Once again, this is a story that traverses national borders. In the United States, thousands of lawsuits were filed, in cases worth billions of dollars in damages, before the tide turned in favour of scientific evidence that the implants did not cause the alleged harms. “Silicone Breast Implant Litigation” (2010) 12:5 *AMA Journal of Ethics* 389–394, online: <https://journalofethics.ama-assn.org/article/silicone-breast-implant-litigation/2010-05>. For a lengthy examination of the implications of these cases around science and the law, albeit with an American legal focus, see Bernstein, David E, “Review: the breast implant fiasco” (1999) 87:2 *California Law Review* 457–510.

⁴⁸⁸ *Medical Devices Regulations* (SOR/98-282), Schedule 1, Part 1, Rule 6.

failed, are unavailable or are unsuitable”.⁴⁸⁹ As such, the SAP for medical devices is notably more flexible, with “emergency use” supplemented by the broader catch-all “or if conventional therapies have failed, are unavailable or are unsuitable”. From a legal perspective, it is thus less surprising that more applications were granted under this more permissive pathway.

There are other differences between the two Special Access Programmes; for instance, instead of an exemption from the regulations, the healthcare provider applies for an authorization.⁴⁹⁰ And once applied for, the Minister has less discretion:

72 (1) The Minister shall issue an authorization referred to in subsection 71(1) to a manufacturer or importer if the Minister determines that

- (a) the benefits that may be obtained by the patient through the use of the device outweigh the risks associated with its use;
- (b) the health or safety of patients, users or other persons will not be unduly affected;
- (c) a licensed device that would adequately meet the requirements of the patient is not available in Canada; and
- (d) the authorization is not being used by the manufacturer or importer to circumvent the requirements of Part 1 [permitting the device to be marketed in Canada].

This is in contrast to the SAP for drugs, which provides the Minister with a discretionary “may” when it comes to issuing a letter of authorization, which in turn is only issued to the practitioner, rather than directly to the manufacturer or importer.⁴⁹¹ It is also the case that later the same year this story broke, silicone breast implants were once more permitted onto the Canadian market, suggesting the possibility that sufficient evidence may have been amassed to satisfy Health

⁴⁸⁹ *Medical Devices Regulations* (SOR/98-282), s.69(2).

⁴⁹⁰ *Medical Devices Regulations* (SOR/98-282), s.71(1).

⁴⁹¹ *Food and Drug Regulations* C.08.010 (1)

Canada on the safety of silicone breast implants before that time.⁴⁹² Nonetheless, the gap between these two Special Access Programmes does seem rather jarring. Despite conflating the two pathways, Christie and Montaner's broader observation about the disparity in ease of access relative to medical importance remains very apt:

One of our patients died during this 10-month battle, but no one has ever died from 'small breasts' or 'slight rippling of the skin.' Without disparaging the difficulties experienced by women who need breast implants, we cannot contain our moral outrage at the ineffectiveness of the SAP in dealing with this truly life-threatening matter.⁴⁹³

These differing standards between the SAPs for drugs and medical devices have been remarked upon elsewhere.⁴⁹⁴ While it has been suggested the broad drafting of the SAP for medical devices may in part reflect intentional policy choices such as its inclusion of custom-made devices, other inconsistencies may "be simply an accidental by-product of drafting the two sets of regulations separately".⁴⁹⁵ At the very least, these differences raise questions about the underlying intent of Health Canada's regulation of health and medical products; it is unclear what policy objective is served by making access to unmarketed medical devices so much easier than pharmaceuticals, especially given the *Food and Drugs Act* is the enabling statute for both sets of regulations. In this particular instance, the fact that the medical device in question was explicitly removed from the market over safety concerns drives home this incongruity. Furthermore, even those restrictions that do appear in the SAP for medical devices do not seem to have been fully observed

⁴⁹² Gandhi, Unnati, "Health Canada approves use of silicone-gel breast implants", *The Globe & Mail* (21 October 2006), online: <<https://www.theglobeandmail.com/news/national/health-canada-approves-use-of-silicone-gel-breast-implants/article654247/>>.

⁴⁹³ Christie, Timothy K S & Julio S G Montaner. "The perverted irony of Health Canada's Special Access Programme" (2006) 174:12 CMAJ 1746.

⁴⁹⁴ See e.g., Maier, Roland K, Devidas Menon & Tania Stafinski, "The Medical Devices Special Access Program in Canada: A Scoping Study" (2018) 13:3 Healthc Policy 40–57.

⁴⁹⁵ Tigerstrom, Barbara von & Emily Harris, "Access to Experimental Treatments: Comparative Analysis of Three Special Access Regime" (2016) 24 Journal of Law and Medicine 119–149.

in this instance. As noted above, the regulations indicate that the Minister shall only issue an authorization if it is determined that “the authorization is not being used by the manufacturer or importer to circumvent the requirements” permitting the product to be marketed in Canada. With this in mind, consider the following academic publication by plastic surgery practitioners framing the effects of access via the SAP on the uptake of silicone breast implants as doing precisely that:

The government of Canada introduced round silicone gel implants to the Canadian market through the Special Access Program in 1999. Anatomical silicone gel implants became available through the Special Access Program in 2000. There has been a large increase in the use of silicone implants by Canadian plastic surgeons since the Special Access Program reintroduced them into the Canadian market in 2000. This increase is consistent across all provinces in Canada. The most dramatic increase in use has been for breast augmentation.⁴⁹⁶

While this is of course an interpretation by the authors of the article rather than an official statement by Health Canada on the market status of these implants, it offers a clear illustration that at least some practitioners consider the SAP to be a form of government-sanctioned market approval rather than an emergency mechanism to access an unmarketed product. The scale of such access makes such an interpretation entirely understandable. At the very least, this disjunct between market regulation and market reality again raises the broader question of what Health Canada’s underlying goals are when it comes to accessing unmarketed health products under the *Food and Drugs Act*.⁴⁹⁷

⁴⁹⁶ Snell, Laura, Nancy Baxter & John L Semple, “A survey of attitudes of Ontario plastic surgeons leading up to the return of silicone implants” (2008) 122:5 *Plast Reconstr Surg* 148e–149e.

⁴⁹⁷ As an aside for those curious, medical leeches and medical maggots have traditionally been accessed via the Special Access Programme for drugs, not for medical devices. The importance of obtaining leeches through the proper channels was highlighted in a disciplinary hearing in *Ontario (College of Traditional Chinese Medicine Practitioners & Acupuncturists of Ontario) v Rea*, 2017 ONCTCMAO 4 (CanLII), online: <<https://canlii.ca/t/hsqnz>>.

The goals of the SAP: the 714-X Case.

The 2006 case of *Delisle v. Canada (Attorney General)* raises further questions about the goals of the SAP that remain unanswered to this day.⁴⁹⁸ It also highlights the need for reform while simultaneously illustrating that the courts may not always be the vehicle for it. While as seen elsewhere in this thesis the SAP has been implicated in the courtroom on multiple occasions, it has almost always been invoked by pharmaceutical companies; *Delisle* is one of the few cases, and certainly the highest profile, to be driven by patients.⁴⁹⁹ As must be recalled, the patient has no direct role in the SAP process, despite their obvious personal stake in the outcome. This case, subsuming four applications for judicial review, does not focus directly on specific requests to the SAP, however. Instead, it challenges an internal SAP policy that was intended to curb longstanding access via the SAP to a “medicine” that was about as far from an Essential Medicine as possible. The “medicine” in question was 714-X.

714-X, more clumsily known as trimethylbicyclonitramineoheptane chloride, is a substance invented by Gaston Naessens, a French national resident in Québec.⁵⁰⁰ It is manufactured in Canada, not imported from abroad. It is not approved by any regulatory authority anywhere in the world. A 1998 review of 714-X in the *Canadian Medical Association Journal* describes it as a “camphor compound that has been chemically combined with extra nitrogen as well as ammonium salts, sodium chloride and ethanol”.⁵⁰¹ Promoted as a treatment for cancer and HIV among other conditions, the theory behind 714-X, per the CMAJ report, is that it disrupts the lifecycle of “somatids”, which are “living organisms distinct from bacteria and viruses” that Naessens detects using “his somatoscope [a

⁴⁹⁸*Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII).

⁴⁹⁹ It also has the distinction of being cited by the European Court of Human Rights. *Hristozov and Others v. Bulgaria* - 47039/11 358/12 - HEJUD [2012] ECHR 1914 (13 November 2012), albeit largely as an illustrative example of foreign practice rather than a particularly influential bit of jurisprudence on its merits.

⁵⁰⁰ Naessens died in 2018. Goupil, Alain, “Le chercheur Gaston Naessens n’est plus”, *Le Soleil* (21 February 2018), online: <<https://www.lesoleil.com/2018/02/21/le-chercheur-gaston-naessens-nest-plus-931d36d770857ca50d52a3f24906114e>>.

⁵⁰¹ Kaegi, E. “Unconventional therapies for cancer: 6. 714-X. Task Force on Alternative Therapeutic of the Canadian Breast Cancer Research Initiative” (1998) 158:12 CMAJ 1621–1624.

special microscope of his own design] to examine fresh blood from healthy individuals and those with various diseases”.⁵⁰² For patients, “714-X is usually administered by injecting it into the lymph nodes in the groin”.⁵⁰³ The CMAJ review ultimately reaches the following somewhat understated conclusion on 714-X:

Its formulation and administration are based on unconventional views about the nature of cancer that have not been substantiated by mainstream researchers. Side effects appear to be minimal, but evidence of its effectiveness is limited.⁵⁰⁴

In the United States, the importation and sale of 714-X has long been banned, leading to at least one criminal conviction on charges of introducing an unapproved drug into interstate commerce.⁵⁰⁵ In Canada, the story is different. As outlined in *Delisle*, the SAP began regularly granting access to 714-X in 1989.⁵⁰⁶ Somewhat stunningly, it began doing so *after* a high-profile criminal trial in which Naessens was acquitted in the death of a cancer patient he had treated with 714-X (he would plead guilty to lesser charges relating to practicing medicine without a licence).⁵⁰⁷ Shortly after the verdict in the case, it became available under the SAP (then the EDRP).⁵⁰⁸ This was accompanied by a bizarre statement from Health Canada in which it expressed concern about growing public attention to 714-X (fueled by the high-profile trial), and emphasized the lack of scientific evidence supporting its

⁵⁰² Kaegi, E. “Unconventional therapies for cancer: 6. 714-X. Task Force on Alternative Therapeutic of the Canadian Breast Cancer Research Initiative” (1998) 158:12 CMAJ 1621–1624.

⁵⁰³ Kaegi, E. “Unconventional therapies for cancer: 6. 714-X. Task Force on Alternative Therapeutic of the Canadian Breast Cancer Research Initiative” (1998) 158:12 CMAJ 1621–1624.

⁵⁰⁴ Kaegi, E. “Unconventional therapies for cancer: 6. 714-X. Task Force on Alternative Therapeutic of the Canadian Breast Cancer Research Initiative” (1998) 158:12 CMAJ 1621–1624.

⁵⁰⁵ *United States of America, Appellee, v. Writers & Research, Inc., Defendant, Charles R. Pixley, Defendant-appellant*, 113 F.3d 8 (2d Cir. 1997).

⁵⁰⁶ *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 30.

⁵⁰⁷ As an illustration of how high-profile it was, multiple public figures, including the French Ambassador and a Member of Québec’s National Assembly testified in support of the product. McLaughlin, Ann, “Jury finds Naessens not guilty in death of cancer patient”, *The Montreal Gazette* (2 December 1989); Legault, Rita, “Naessens fined after admitting illegal practice”, *The Montreal Gazette* (14 June 1990).

⁵⁰⁸ Dunn, Kate, “Naessens’s elixir to be made available; Federal officials stress they’re not endorsing 714-X serum”, *The Montreal Gazette* (25 January 1990).

use.⁵⁰⁹ In making this latter point, it states not merely that it “does not have any medical evidence to support the claim of usefulness of 714X in the treatment of AIDS or cancer” but that “the Expert Advisory Committee on HIV Therapy to the Health Protection Branch unanimously deplored the use of 714X for the treatment of cancer and human Immunodeficiency Virus (HIV)-related disease including AIDS”.⁵¹⁰ Putting it lightly, this pronouncement does not exactly reflect the evidentiary standard a physician is generally required to meet when attempting to access a drug via the SAP.

Over a decade later, according to the decision in *Delisle*, a new internal SAP policy was created stating that access to 714-X would be limited in the future. All four patients were concerned about this new policy and had physicians who had previously requested 714-X under the SAP.⁵¹¹ Of the four patients, two were currently receiving 714-X via the SAP, one previously had access but longer did, and one had never received access. The relevant portion of the policy, contained in a letter that was sent to physicians, is as follows:

Based on a further review of evidence now available with respect to the use, safety and efficacy of this drug, as they relate to the emergency uses for which this drug has been requested, it has been determined that significant new evidence would have to be included in any SAP request before any further sales of 714-X could be authorized pursuant to requests made under section C.08.010 of the *Food and Drug Regulations*. Given this determination, it is unlikely that the SAP will authorize the sale of 714-X for new patients. During an interim period of one year, the SAP will take account of the special considerations relating to patients currently receiving the drug, who in the opinion of the practitioner have not experienced adverse effects from their

⁵⁰⁹ Health & Welfare Canada (Health Protection Branch), “714-X: an unproven product” (1990) H50-3/23-1990E.

⁵¹⁰ Health & Welfare Canada (Health Protection Branch), “714-X: an unproven product” (1990) H50-3/23-1990E.

⁵¹¹ *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 38.

ongoing treatment, and may continue to authorize requests made for such patients. The SAP then will revisit the merits of any such continued authorizations on the basis of reports filed on the previous use of the product, including any adverse events, in accordance with subparagraph C.01.010 (b)(i) of the Food and Drug Regulations.⁵¹²

The letter goes on to recommend that a clinical trial for 714-X would be the most appropriate means of access, as well as being in the best interests of the patients.⁵¹³ In response, the applicants in *Delisle* raised a range of issues relating to jurisdiction and the scope of discretionary power. They also contended this policy change was a breach of legitimate expectation, as “after 15 years of access, they had a legitimate expectation that their requests for access would be authorized”.⁵¹⁴ Furthermore, they put forward an alternative argument seeking that the Court declare the sections of the *Food and Drug Regulations* underpinning the SAP to violate sections 7 (liberty and security of the person) and 15 (equality) of the Canadian Charter of Rights and Freedoms.⁵¹⁵ Ultimately, the Court rejected the vast majority of claims, including those relating to legitimate expectation and to *Charter* violations, but found that the new guideline unduly fettered the discretionary power afforded to the SAP.⁵¹⁶ The judge’s reasoning, in four parts, was as follows:

Firstly, the SAP was created in an attempt to strike a balance between access to medication that has not yet proven itself and humanitarian reasons in the case of an illness for which the conventional treatments were ineffective or inadequate. In my opinion, the January 23, 2004 public policy does not reflect the balance sought by Parliament, because it does not take into consideration humanitarian or compassionate concerns.

⁵¹² Quoted in *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 38.

⁵¹³ Quoted in *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 38.

⁵¹⁴ *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 3.

⁵¹⁵ *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 14.

⁵¹⁶ *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 172.

Secondly, the public policy requires a clinical trial for 714-X before any discretionary power may be exercised.

Thirdly, with regard to new patients, the access door, for all intents and purposes, is shut. All requests for access on hold for new patients were denied on January 23, 2004 because they had not been treated with 714-X. The humanitarian factor was not taken into account.

Fourthly, the same fate awaits the old patients at the end of the interim period. My finding is not harmful for Health Canada and the SAP. It simply requires a weighing of the valid objectives of the public policy against the humanitarian factor.⁵¹⁷

This decision was criticized by experts who perceived it as promoting access to an implausible product in the complete absence of scientific evidence.⁵¹⁸ Its fallout has been minimal in practice, primarily because the decision itself is actually fairly narrow, focusing on the specific policy that would have ended requests for 714-X rather than SAP practice more generally. However, it does raise some troubling questions about both the SAP itself, and how it is assessed in the courtroom.

The intended goals of the SAP will be revisited in more depth shortly, including the issue of humanitarian considerations. However, this decision goes beyond any reasonable interpretation of such purposes. Regardless of any “balance sought by Parliament” as referenced by the judge, there is simply no evidence to suggest Parliament intended that the scales should tip in favour of long-term access to an unapproved product lacking not only any credible evidence of efficacy but any remotely plausible scientific basis. At the same time, prior to the implementation of the internal policy, this does seem to have regularly been the outcome for requests for 714-X under the SAP. The reasons for this remain unclear. The decision notes Naessens “submitted an affidavit in support of each application for judicial review

⁵¹⁷ *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 173-177 [paragraph numbers removed].

⁵¹⁸ Blackwell, Tom, “Ottawa opens door to unproven treatments”, *The National Post* (21 October 2006).

and was not cross-examined”.⁵¹⁹ As quoted in the decision, Naessens states in his affidavit that up until March of 2004, “1,499 Canadian physicians received 20 985 authorizations from Health Canada for 714-X, which is the equivalent of 440,685 injections and 30,513 treatments by inhalation provided for 4,051 Canadian patients”.⁵²⁰ Although no further evidence for these figures is provided, they were, as noted, not contested in court. Given not only that 714-X lacks scientific evidence of its utility (including a total absence of clinical trials for any indication), but that its mechanism of action also defies common sense, this level of access, or even a level remotely approaching it, does not reflect well on the SAP evaluation process, particularly when other applications for Essential Medicines are regularly declined.

Of course, the lack of evidence supporting 714-X for any indication also raises some questions about the nearly 1500 physicians alleged to have requested it. As testimony from the SAP indicates, early interest in 714-X had been for HIV, at a time when no effective treatments were available; interest “waned precipitously” for that indication once other (effective) treatments became available.⁵²¹ In the absence of any truly effective treatments, a purely humanitarian argument may seem more compelling; as will be seen shortly, access to HIV treatment had a major influence on Canadian policy governing access to unapproved drugs more generally. Nonetheless, this is also a reminder that the SAP – in theory – is supposed to play a useful gatekeeping role, one that is preferable to permitting physicians to simply access any drug for any purpose. In this case, a Health Canada Expert Committee had “unanimously deplored the use of 714X for the treatment of cancer and human Immunodeficiency Virus (HIV)-related disease including AIDS” over a decade before.⁵²² No compelling evidence of its utility had emerged since that statement. As such, the disjunct between access to 714-X and access to Essential Medicines recognized as the standard of care raises real questions about how effective the SAP is in fulfilling this gatekeeping role in practice.

⁵¹⁹ *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 29.

⁵²⁰ *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 30.

⁵²¹ Testimony of Ian MacKay, Director of the SAP, quoted in *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 78.

⁵²² Health & Welfare Canada (Health Protection Branch), “714-X: an unproven product” (1990) H50-3/23-1990E.

Amazingly, in the wake of *Delisle*, requests for 714-X have continued to be granted by the SAP, even though no clinical trials have been published in the peer-reviewed medical literature in the interim; ironically, in 2013, the same number of requests (23) were approved for 714-X as for cycloserine.⁵²³ Perhaps some of this ongoing access can be traced to the fact that in 2008, Canada entered into a settlement agreement with Delisle (the individual plaintiff), under the terms of which Health Canada agreed to follow the court's recommendations [in the case discussed above] "with regards to the administration of the SAP when dealing with 714-X", in exchange for Delisle dropping a class action lawsuit around access to 714-X.⁵²⁴ That said, agreeing not to restrict the discretion of SAP decision makers is one thing; maintaining a system in which that discretion is regularly exercised in favour of continued access to 714-X even in the utter absence of scientific evidence is quite another, particularly when requests for Essential Medicines are being denied. Under the circumstances, fettering SAP discretion via explicit integration of reference points like the WHO MEML might be helpful for ensuring access to the standard of care, but may still not resolve all issues in the decision-making process.

Further exacerbating the situation is the fact the continued approval of requests for 714-X via the SAP has further undermined any ostensible goals of ensuring unapproved products are not marketed. As of this writing, Cerbe Distribution, the Sherbrooke-based manufacturer and distributor of 714-X, continues to state on their website that "714X has been legally available in Canada since 1989 via a special access program sponsored by the Canadian government".⁵²⁵ On its order page, it states that in Canada "access to 714X is available through the Special Access Program (SAP) since 1989 under the

⁵²³ Houston, Adam R et al., "Reforming Canada's Special Access Programme (SAP) to improve access to off-patent essential medicines" (2018) 3:2 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 100–107, online: <<http://jammi.utpjournals.press/doi/10.3138/jammi.2018.01.04>>.

⁵²⁴ "Settlement agreement between Léopold Delisle (Plaintiff) and Attorney General of Canada and Department of Health (Health Canada) and Director General Therapeutic Products Directorate (Health Canada) (Defendants)", File T-220-04 (2008), online: <<http://lbalavocats.ca/documents-recours/medicaments/termes/714x/an/settlement%20agreement.pdf>>.

⁵²⁵ Cerbe Distribution, "Frequently Asked Questions 714-X" (2021), online: <<https://www.cerbe.com/faq-page>>.

patronage of Health Canada (articles C.08.010 and C.08.011 of the Food and Drug Regulations - C.R.C., c.870)".⁵²⁶ Access through the SAP, and the regulations underpinning it, are thus openly used to advertise the "patronage" of Health Canada. Ultimately, it is troubling that the primary case to address patient access via the SAP did not redress a failure to provide an established Essential Medicine accepted as the standard of care, but instead focused on maintaining access to a "medicine" of no demonstrated utility.⁵²⁷ As illustrated thus far, the SAP is not an effective tool for accessing Essential Medicines accepted as the standard of care; it is also not a useful tool for bringing unmarketed Essential Medicines to market. Now it appears it is also not up to the task of preventing access to products of no demonstrated medicinal value. What, then, is the SAP intended to do?

Purpose and evolution from the EDRP to the SAP

In *Delisle*, the judgement states that the SAP "was created in an attempt to strike a balance between access to medication that has not yet proven itself and humanitarian reasons in the case of an illness for which the conventional treatments were ineffective or inadequate".⁵²⁸ By this standard, ensuring access to Essential Medicines of proven utility that form the conventional standard of care around the world would be the only humanitarian thing to do. In reality, as noted earlier, four out of fourteen Essential Medicines contained in the Interagency Emergency Health Kit – a globally recognized tool explicitly designed to respond to humanitarian emergencies – are not only unavailable in Canada but unreliably available via the SAP. At the very least, this indicates that the SAP is not the right tool for this job.

In truth, it is not clear how the judge reaches this conclusion about the purposes of the SAP, or where the heavy emphasis on "the balance sought by

⁵²⁶ Cerbe Distribution, "Order" (2021), online: <<https://www.cerbe.com/order>>.

⁵²⁷ As a brief postscript, this case was cited in passing, as noted earlier, by the European Court of Human Rights in *Hristozov and Others v. Bulgaria* - 47039/11 358/12 - HEJUD [2012] ECHR 1914 (13 November 2012); however, in *Hristozov*, the Court ruled in favour of the government and against access. Ironically, that case involved access to another unapproved cancer treatment of dubious utility produced by a Canadian company, MBVax Coley Fluid made by MBVax Bioscience Inc.

⁵²⁸ *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 173.

Parliament” that must “take into consideration humanitarian or compassionate concerns” comes from.⁵²⁹ For one, the SAP is a regulatory creature, and as such does not directly reflect Parliamentary intent. For another, these notions cannot be drawn directly from the underlying regulatory framework of the SAP, which contains no reference to humanitarian or compassionate use. At best, the idea can be inferred from the grant of permission to access an unapproved drug in an emergency; however, even here it is clear the governing regulations were primarily a pragmatic measure intended as a temporary bridge to access medicines with some evidence of utility, such as those already marketed elsewhere, rather than a means to simply brush aside the regulatory purposes of the *Food and Drugs Act* to permit access to products with no possibility of meeting formal regulatory requirements.⁵³⁰

Ultimately, the perspective in the *Delisle* decision may be explained by a reference it *does* include a citation for: The 1996 report from the Parliamentary Standing Committee on Health’s Sub-Committee on HIV/AIDS entitled *Compassionate Access to Investigational Therapies*.⁵³¹ While the focus of the HIV Sub-Committee Report reflects its title, it sheds light upon the evolution of the policy framework for accessing unapproved medicines as the EDRP became the SAP.⁵³² It must be emphasized that this transition was one of policy, not of underlying law; indeed, the shift from the EDRP to the SAP involved no changes to the underlying regulations at all, making it difficult to argue a shift in regulatory intent. Nonetheless, the HIV Sub-Committee Report remains the most detailed exploration of the purposes of the SAP and its underlying regulations.

⁵²⁹ *Delisle v. Canada (Attorney General)*, 2006 FC 933 (CanLII) at para. 173.

⁵³⁰ See “Regulations Amending Certain Regulations Made Under the Food and Drugs Act (Sale of a New Drug for Emergency Treatment): SOR/2020-212”, Canada Gazette, Part II, (14 October 2020), Volume 154, Number 21, online: <<http://www.gazette.gc.ca/rp-pr/p2/2020/2020-10-14/html/sor-dors212-eng.html>>.

⁵³¹ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996).

⁵³² Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996).

While this transition between the EDRP and the SAP was to a large extent a change in name, it took place against the backdrop of major shifts in the *kind* of unapproved drugs that were being accessed, as well as bolder, ultimately unrealized, proposals to improve access to them. As the involvement of the HIV Sub-Committee suggests, this transition was heavily influenced by HIV. This is unsurprising. More so than any other disease of the modern era, HIV has been a powerful motivator for changes to law and policy, particularly around pharmaceuticals. It has played a crucial role in driving the evolution of access to medicines in arenas ranging from boardrooms to courtrooms, and in legal fields from intellectual property to human rights.⁵³³ Along the way, the WHO MEML itself would evolve in response to HIV, expanding its ambit to include newer drugs still under patent, after decades of focusing on off-patent drugs.⁵³⁴ However, even before it drew attention towards patented new drugs at the international level, HIV served to put the issue of access to unapproved investigational drugs in the spotlight.⁵³⁵

It is clear that HIV had already impacted the EDRP by the time the HIV Sub-Committee delved into the issue. A 1991 report singles out the early HIV drug AZT as one that “rocked” Canadian approaches to accessing unapproved drugs prior to its approval.⁵³⁶ The HIV Sub-Committee Report observes that the EDRP “covers two therapeutic categories: investigational drugs and drugs approved in foreign countries”. In turn, it notes that when “the EDRP was established in 1966, it was

⁵³³ These are areas that have been widely studied, and a comprehensive review is well beyond the scope of this thesis. For an example of a landmark human rights decision around access to medicines, see the South African case of *Minister of Health and Others v Treatment Action Campaign and Others* (No 2) (CCT8/02) [2002] ZACC 15; 2002 (5) SA 721; 2002 (10) BCLR 1033 (5 July 2002). For intellectual property, access to antiretrovirals was the driving force behind the World Trade Organization’s “Doha Declaration”, more formally known as the Declaration on the TRIPS Agreement and Public Health, (14 November 2002), WT/MIN(01)/Dec/2.

⁵³⁴ This shift was particularly obvious in 2002. WHO Expert Committee on the Selection and Use of Essential Medicines, ed, *The selection and use of essential medicines: report of the WHO expert committee, 2002*; WHO Technical Report Series 914 (Geneva: World Health Organization, 2003).

⁵³⁵ There is considerable literature in this area, particularly from the United States. Given the focus on experimental drugs, it is largely beyond the scope of this thesis. For an interesting historical example, see Levi, Jeffrey, “Unproven AIDS Therapies: The Food and Drug Administration and ddi” in *Biomedical Politics* (Kathi E Hanna, ed.) (Washington, D.C.: National Academies Press, 1991).

⁵³⁶ Clark, Edie & Canadian Coordinating Office for Health Technology Assessment, *A Survey of investigational new drug and emergency drug release policies* (Ottawa, Ont.: Canadian Coordinating Office for Health Technology Assessment, 1991) at p.30.

largely used for this latter function; however, since the emergence of the AIDS epidemic approximately 15 years ago, the focus of the EDRP has shifted to the point where the authorization of experimental drugs for people who are catastrophically ill is the program's major function".⁵³⁷ Such experimental drugs were being released in large volumes; by 1995, the CMAJ reported that the program was approaching 50,000 requests annually.⁵³⁸ The result was that discussion of EDRP reform, exemplified by the HIV Sub-Committee Report, was far more focused on the emerging "investigational drugs" side of the equation than the longstanding "drugs approved in foreign countries" side. The fact that, in the earliest years of HIV in Canada, an antimalarial had been the most requested drug goes unremarked upon.⁵³⁹ Ironically, this Sub-Committee report was released in 1996, the year that Highly Active Antiretroviral Therapy (HAART), the first truly effective treatment for HIV, emerged; as a consequence, the most prominent issue around access to medicines for HIV would shift from access to experimental drugs to affordable access to approved, effective medicines.⁵⁴⁰ Had the report been written a few years earlier, or a few years later, its focus might have been different; on the other hand, without the catalyst of HIV, it might not have been written at all.

That the prevailing circumstances meant laws and regulations were being stretched beyond their traditional interpretations is readily apparent, from the shift in EDRP use to the HIV Sub-Committee Report's suggestion that "it can be argued that the government has an obligation to catastrophically-ill Canadians to do all that is reasonable to promote and preserve their health".⁵⁴¹ Even as it does

⁵³⁷ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996).

⁵³⁸ Robinson, A. "Requests approaching 50,000 annually for emergency drug release program" (1995) 153:5 CMAJ 665-666.

⁵³⁹ White, G F & MJ Davis, "Antiparasitic drugs: availability and regulatory requirements for 'emergency' supply" (1985) 132:3 Can Med Assoc J 273-274.

⁵⁴⁰ See e.g., Zuniga, José M et al., *A Decade of HAART* (Oxford University Press, 2008).

⁵⁴¹ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996). This argument is premised on the Minister's mandate under what was then the *Department of National Health and Welfare Act*. A similar argument can be drawn from the current *Department of Health Act* (S.C. 1996, c. 8), particularly subsections 4(2)(b) and (d).

so, the HIV Sub-Committee Report acknowledges that “catastrophic rights do not have the force of legal recognition in Canada”, thus raising questions about how far such an obligation could be stretched.⁵⁴² As a result of the central focus on experimental drugs for HIV, many points of contention in the HIV Sub-Committee Report and surrounding discussions are of greater concern for experimental treatments than well-established Essential Medicines. For instance, the issue of the impact of access to experimental drugs on clinical trials receives considerable attention. This was already a high-profile topic in policy circles; for instance, by this point Gil and colleagues had gone so far as to warn that the “compassionate release of drugs for HIV infection could become the paradigm process that corrodes and corrupts the ethical and scientific validation of new pharmaceuticals in Canada”.⁵⁴³ This debate pitting immediate access against the scientific method, while intriguing, is largely outside the bounds of a thesis focused on drugs already in longstanding use; clinical trials are far less of a concern when patients are being treated with Essential Medicines that have been the standard of care for decades.⁵⁴⁴ Nevertheless, despite the focus on experimental drugs, the HIV Sub-Committee Report also illustrates the need for broader reforms for accessing unapproved drugs.

Ultimately, the idea of scrapping the EDRP entirely was rejected. As the head of the EDRP explained matters in practical terms the year before the HIV Sub-Committee Report, without making reference to humanitarian or compassionate

⁵⁴² Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996). Catastrophic rights had been a matter of discussion for some time. See e.g., Dixon, John Edward, *Catastrophic rights: experimental drugs & AIDS* (Vancouver: New Star Books, 1990); Russell, John, “Access to Experimental Therapies and AIDS” (1991) 30:3 Dialogue 399–418, online: https://www.cambridge.org/core/product/identifier/S0012217300011744/type/journal_article >.

⁵⁴³ Gill, M John, Michael M Burgess & T Douglas Kinsella. “Ethical modifications of the Emergency Drug Release Program for AIDS: a proposal” (1992) 146:9 CMAJ 1541–1545.

⁵⁴⁴ For some further perspectives at the time, see e.g., Richman, D D, “Public access to experimental drug therapy: AIDS raises yet another conflict between freedom of the individual and welfare of the individual and public” (1989) 159:3 J Infect Dis 412–415; Russell, John, “Access to Experimental Therapies and AIDS” (1991) 30:3 Dialogue 399–418, online: https://www.cambridge.org/core/product/identifier/S0012217300011744/type/journal_article >.

considerations: “As long as drug companies do not market all their drugs in Canada and it takes some time for new drugs to be evaluated and approved, a program to release nonmarketed drugs will be needed”.⁵⁴⁵ Such a program would indeed remain in place; it would be re-christened the Special Access Programme. Even with the disproportionate attention to experimental access at the time, the SAP as originally envisioned took a broader approach to access that would have, if enacted, proactively addressed concerns raised elsewhere in this thesis. As summarized in the HIV Sub-Committee Report, some major reforms were on the table:

The Drugs Directorate examined the EDRP and found it to be very labour and time intensive for both physicians and EDRP personnel. Further, there is the concern that the action of providing legal access to an unmarketed drug gives the erroneous impression that Health Canada is actually endorsing the efficacy and safety of the drug. To help correct these problems, the Drugs Directorate has proposed a replacement program called the Special Access Program (SAP). This program recognizes two categories under which unmarketed drugs may be legally obtained, first in an emergency situation, and secondly for a situation where the drug can be expected to maintain or extend quality of life.⁵⁴⁶

In the first of these scenarios, responding to an emergency situation, some of the proposed aspects of the SAP were quite different from what ultimately emerged. For instance, one proposal would have allowed a manufacturer to apply for a certificate permitting emergency sale to multiple practitioners for a particular

⁵⁴⁵ Robinson, A. “Requests approaching 50,000 annually for emergency drug release program” (1995) 153:5 CMAJ 665–666.

⁵⁴⁶ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996), Appendix II.

emergency, rather than on an individual patient basis.⁵⁴⁷ Another even bigger reform would have involved largely removing Health Canada from the equation, serving to “cut the directorate out of the loop on each approval and allow physicians to deal directly with drug companies”.⁵⁴⁸ It was also suggested that removing Health Canada from the process would mitigate the risk of Health Canada being perceived as endorsing the efficacy and safety of the drug. Removing Health Canada’s Drugs Directorate from case-by-case involvement was thus highlighted by the government as a major advantage for Health Canada.⁵⁴⁹ The Executive Director of the Drugs Directorate within Health Canada stated that “44 000 discussions with physicians each year isn’t the best use of the directorate’s resources”.⁵⁵⁰ As such, the emergency portion of the SAP was proposed as follows:

Under the proposed SAP, an emergency situation is when the patient is seriously ill with a condition from which serious deterioration of the patient is reasonably likely to occur, or from which premature death is reasonable likely to occur, in the absence of immediate or early treatment. In this situation, the Drugs Directorate feels that its involvement is unnecessary and may, in fact, interfere with the speed in which the drug may be provided. Instead, it would be the physician’s responsibility to determine if the situation is an emergency and to contact the manufacturer to obtain the unmarketed drug. The manufacturer would be required to notify the Drugs Directorate of all emergency releases within 48 hours of release, including the name of the drug, the indication for use,

⁵⁴⁷ Gilron, I. “The Emergency Drug Release Program: regulatory aspects of new drug access in Canada” (1993) 148:7 CMAJ 1151–1153; Robinson, A. “Requests approaching 50,000 annually for emergency drug release program” (1995) 153:5 CMAJ 665–666.

⁵⁴⁸ Robinson, A. “Requests approaching 50,000 annually for emergency drug release program” (1995) 153:5 CMAJ 665–666.

⁵⁴⁹ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996).

⁵⁵⁰ In fairness, many of those physicians likely felt exactly the same way. Robinson, A. “Requests approaching 50,000 annually for emergency drug release program” (1995) 153:5 CMAJ 665–666.

quantity of drug released, and the physician's name. The physician would also be required to notify the Directorate within 48 hours about the use of the drug.⁵⁵¹

In addition to this emergency scenario in which the physician approached the company directly without the involvement of Health Canada, it was proposed the SAP would also encompass a second scenario, taking steps to address access in *non-emergency* situations. In such situations, where there was no emergency but “where quality of life might be maintained or improved by an unmarketed drug”, then “a different mechanism would apply”.⁵⁵² In this latter instance, an application could be made for bulk authorization for up to 50 patients; if the drug was released, physicians would have a responsibility to report to the company, who in turn would be responsible for reporting information such as adverse effects to the Drug Directorate.⁵⁵³ However, in non-emergency situations an application for a drug could also be denied with a recommendation for a formal clinical trial.⁵⁵⁴

The astute reader will have noticed that these proposals are not reflected in the Special Access Programme as it has been described thus far. This is true: While the EDRP became the SAP, most of these more drastic changes were ultimately not part of that transition. Had they been, some of the problems with the current SAP might have been avoided. Instead, the reforms were scaled back, and these concerns would persist for a quarter century. It must also be said, however, that some of the proposed reforms could have created new issues of their own; for instance, removing a Health Canada gatekeeping function entirely might have

⁵⁵¹ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996), Appendix II.

⁵⁵² Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996), Appendix II.

⁵⁵³ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996), Appendix II.

⁵⁵⁴ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996), Appendix II.

served to facilitate use of dubious products like 714-X just as readily as to improve access to Essential Medicines. Indeed, removing Health Canada oversight entirely would have been at even greater odds with the premise of pharmaceutical regulation under the *Food and Drugs Act*.

The HIV Sub-Committee Report also offers a rare window into the legal guidance Health Canada has seemingly relied upon in relation to other aspects of access to unmarketed drugs. In particular, it offers insights in relation to the ability of a company to refuse to supply a drug via the SAP even after Health Canada has granted permission. Here, the Sub-Committee turned to the testimony of Mario Simard, legal counsel for Health Canada. Simard “indicated that there was no known incidence where legal action was ever taken against the government because of authorized compassionate release of an experimental therapy”.⁵⁵⁵ This suggests that the issue of government liability for products released under the SAP was a hypothetical concern rather than an everyday problem. The potential liability discussion then turned to that of the manufacturer for any damage caused by its product; this was highlighted as the justification for leaving the ultimate decision on release to the manufacturer.⁵⁵⁶ Here, Simard also expresses the view that government liability would itself change in the event that legislation compelled pharmaceutical companies to distribute investigational drugs and the patient was harmed as a result, particularly if the company did so against its better judgement.⁵⁵⁷ Furthermore, he suggests, where a company did *not* release the drug, the government might face liability for not enforcing the order. Finally, Simard stresses that – as detailed earlier in this thesis – the *Food and Drugs Act* is linked to the federal criminal power under the Constitution, with the purpose of prohibiting

⁵⁵⁵ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996). This appears to hold true today.

⁵⁵⁶ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996).

⁵⁵⁷ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996).

the sale or marketing of dangerous products and regulating their distribution.⁵⁵⁸ As such, he explains, compelling the release of a drug would require amending the *Food and Drugs Act* to include a requirement contrary to the very purposes of the Act.⁵⁵⁹

Given its actions over the next two decades, it appears Canada has generally continued to follow similar advice. In the broader context of pharmaceutical regulation, this is probably sensible. Regardless of any other legal implications, forcing a company to sell a drug the government itself has not approved also seems a rather roundabout approach to the access issue. The government forcing a company to supply an unapproved drug would simply result in the omission of the very government-mandated steps that are intended to establish safety, efficacy and quality. Still, it should be noted that Simard's conclusions were drawn in the context of a discussion focusing heavily on experimental drugs. There is nothing in the HIV Sub-Committee Report to suggest that explicit consideration was ever given in this context to established Essential Medicines that have spots on the WHO MEML, a place in Canadian treatment guidelines, foreign regulatory decisions to draw upon, and years of clinical experience. For such far-from-experimental drugs, not only are the potential benefits more predictable, but any risks to the patient should be, if not necessarily lower, at least better understood. This should shift any liability questions, for all parties concerned, away from guessing at unknowns towards assessing known risks. The idea of compelling companies to provide unmarketed standard of care drugs is certainly not risk-free, but is still one that should be easier to navigate, should the government ever consider furtively testing the waters of pushing companies to make unapproved drugs available. At the same time, such actions would still serve to undermine the purposes of the Act. Furthermore, if the government wishes to push pharma companies, it would make greater sense to find a way to push the drugs all the way onto the formal market.

⁵⁵⁸ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996).

⁵⁵⁹ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996).

Nevertheless, the HIV Sub-Committee Report actually does go so far as to examine whether the government maintains any leverage that might be used to compel companies to provide unmarketed drugs, or to bring them formally to market. As part of this examination, it explicitly addresses a rather bold proposal that had arisen during hearings: that the government either revoke patents or “take away the marketing rights for another product that the company sells in Canada” where a company does not grant access.⁵⁶⁰ This notion is actually granted an entire (albeit brief) appendix to the report. The first element of this proposal, revoking a patent, is rejected promptly, a conclusion grounded primarily in existing treaty obligations.⁵⁶¹ The second element, however, is afforded somewhat more consideration. As the HIV Sub-Committee Report states:

At first consideration, this response does not sound unreasonable, however, who decides which notice of compliance will be revoked? Who takes responsibility for the decision that a cream to treat psoriasis will be taken off the market rather than an ointment for ring-worm if the parent company refuses to grant compassionate access to its experimental cancer drug? Who makes the moral decision which physical ailments will be pitted against each other?⁵⁶²

The acknowledgement that the proposal “at first consideration... does not sound unreasonable” is intriguing; it is hard to imagine the pharmaceutical

⁵⁶⁰ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996), Appendix III Problems associated with revoking either a patent or a notice of compliance.

⁵⁶¹ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996), Appendix III Problems associated with revoking either a patent or a notice of compliance.

⁵⁶² Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996), Appendix III Problems associated with revoking either a patent or a notice of compliance.

lobby agreeing with this assessment. Nevertheless, this section of the report concludes once again that the central premise of pharmaceutical regulation under the *Food and Drugs Act* is about keeping certain drugs away from Canadians, not ensuring access to them:

It was noted that this proposal is in opposition to the spirit of the *Food and Drugs Act*. The Act prohibits the sale of drugs that are not of proven safety and efficacy. Further, it would be in violation of The Department of Health and Welfare Act, in that it would hinder the ability of the Minister to promote and preserve the health of Canadians.⁵⁶³

Given the invocation of the HIV Sub-Committee Report in *Delisle*, there is some further irony to the fact that even the boldest of the reforms contemplated – but not enacted – in transitioning from the EDRP to the SAP fall short of incorporating explicit humanitarian considerations. In fact, the report itself, despite being drawn upon in the *Delisle* judgement, only mentions the term “humanitarian” once, and then only as part of a quote from a witness referring to the moral obligations of pharmaceutical companies, not the goals of the EDRP/SAP.⁵⁶⁴ In truth, issues around bureaucracy and liability seem to be the primary considerations voiced by the government. As such, while humanitarian concerns were certainly a big part of the broader zeitgeist around HIV treatment, it is not at all clear that explicit humanitarian considerations around access to drugs – let alone products like 714-X completely unsupported by scientific evidence – can actually be imputed to the policy goals of the SAP to the extent the *Delisle* decision suggests. If anything, the

⁵⁶³ *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996), Appendix III Problems associated with revoking either a patent or a notice of compliance.

⁵⁶⁴ *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996).

HIV Sub-Committee Report underscores how the existing regulatory goals of the pharmaceutical legislative regime, and the criminal law power it is rooted in, are not compatible with simply throwing open the doors to access. In cold light of day, although the 1996 HIV Sub-Committee Report is probably the most detailed exploration of the goals of the EDRP/SAP, it leaves questions unanswered. Furthermore, even though some big ideas were discussed, comparatively few of the mooted EDRP/SAP reforms were ultimately acted upon at the policy level whilst transitioning between the acronyms; at the regulatory level, things were left entirely unchanged. Despite its evident awareness of many of the problems with the EDRP/SAP, the government ultimately chose not to take many of the bolder steps initially proposed, leaving existing concerns to fester, and Essential Medicines for Neglected Diseases in limbo.

Chapter 6: Off-patent Essential Medicines for Neglected Diseases in the USA

Access in HICs

Although Canada remains the primary focus of this thesis, it must also be emphasized that Canada is affected by broader global trends in terms of both diseases and the drugs to treat them. Furthermore, other high-income countries are experiencing their own domestic variations on access barriers to off-patent Essential Medicines for Neglected Diseases. As but one example, consider Switzerland, the seat of the World Health Organization, and home to major pharmaceutical companies like Novartis and F. Hoffmann-La Roche AG (“Roche”). It too has been affected by the absence of Essential Medicines necessary to respond to emerging patterns of Neglected Diseases, such as the antimalarial drug primaquine, which is not approved for sale in Switzerland, even as the number of imported cases of *P. vivax* malaria has doubled in recent years.⁵⁶⁵ Illustrating that there is no completely accurate predictor for where an Essential Medicine for a Neglected Disease is or is not available, primaquine is marketed in Canada (and has been since 1945). This is just one example of barriers other HICs face in accessing off-patent Essential Medicines for Neglected Diseases. However, the most influential country, in terms of media attention to high-profile barriers, of attempted solutions, and of impacts on access beyond its borders is also Canada’s closest neighbour.

⁵⁶⁵ This increased need is not due to global warming turning alpine meadows into malarious swamps, but new patterns of migration that led to the number of imported malaria cases doubling over the average of the preceding decade. Eperon, Gilles et al., “Malaria cases in Switzerland from 2005 to 2015 and recent rise of imported *Plasmodium vivax* malaria” (2017) 147:4142 *Swiss Med Wkly*, online: <<http://doi.emh.ch/smw.2017.14510>>. One trait of the *P. vivax* parasite is that it can go dormant, only for relapse to occur; for a long time, the only drug available to address *P. vivax* relapse has been primaquine, which has been on the WHO MEML since its inception. Like artemisinin, it was the result of wartime government research during a window when research into treating an otherwise neglected condition was prioritized, this time by the United States as part of their antimalarial research in World War II. Ashley, Elizabeth A, Judith Recht & Nicholas J White, “Primaquine: the risks and the benefits” (2014) 13 *Malar J* 418. While once again not a perfect drug – most famously, it can cause serious issues in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency, thus requiring G6PD testing before administration – it remains an Essential Medicine. Recht, Judith, Elizabeth A Ashley & Nicholas J White, “Use of primaquine and glucose-6-phosphate dehydrogenase deficiency testing: Divergent policies and practices in malaria endemic countries” (2018) 12:4 *PLoS Negl Trop Dis* e0006230.

Comparing Canada's healthcare system to the United States is a national pastime on par with ice hockey (and probably actively participated in by more Canadians). As the world's most lucrative national pharmaceutical market, a number of the Essential Medicines for Neglected Diseases unavailable in Canada, like cycloserine and albendazole, are marketed in the United States. However, despite their formal presence on the market, access barriers have manifested in new ways, which have not only affected access in the US, but spilled over into other jurisdictions, including Canada. These barriers have in turn drawn increased public and political attention to the particular challenges facing off-patent Essential Medicines for Neglected Diseases.

The CDC Drug Service Formulary

Even in the world's most lucrative market, however, there are Essential Medicines that are not available commercially at all. The result has been an unusual but longstanding situation that not only departs from the commercially driven approach so closely associated with access to medicines in the United States, but underscores the inherent failure of reliance on market forces to ensure access to medically valuable but insufficiently profitable medicines. For decades, the American government has made a small number of unapproved drugs of high medical importance available at no cost through the Drug Service of the US Center for Disease Prevention and Control (CDC). These drugs are found on the CDC Drug Service Formulary ("CDC Formulary").⁵⁶⁶ This is in itself quite remarkable; in a country notorious for untameable pharmaceutical pricing, access to these drugs that the invisible hand of the market has failed to provide is nonetheless considered so important for health that they are provided for free by the government. The vast majority of the drugs accessed via the CDC Drug Service are off-patent Essential Medicines for Neglected Diseases.⁵⁶⁷ Some of these Essential

⁵⁶⁶ CDC Drug Service formulary, online:

<<https://www.cdc.gov/laboratory/drugservice/formulary.html>>.

⁵⁶⁷ As of April 2022, they include: diethylcarbamazine for lymphatic filariasis; intravenous artesunate for malaria (though this will change soon given recent FDA approval); diphtheria antitoxin; and eflornithine, melarsoprol and suramin for African trypanosomiasis. The remaining

Medicines, like eflornithine and diethylcarbamazine, were once marketed in the US before being discontinued; others have never been submitted for FDA approval.⁵⁶⁸ Some drugs in this latter category have been on the CDC Formulary for a very long time; for instance, a comparison with the 1974 offerings of the Drug Service's predecessor, the CDC's Parasitic Disease Drug Service, shows a quarter of the drugs are still on the list nearly fifty years later.⁵⁶⁹ In other words, they remain important enough to use, but not lucrative enough to sell.

The CDC Formulary adopts an interesting regulatory approach to access. To get around the issue of market approval, access is premised upon maintaining an open Investigational New Drug (IND) protocol for each drug.⁵⁷⁰ Each of these drugs are treated as an ongoing series of Investigational New Drug (IND) trials, with distribution to each patient justified as being single patient (N=1) trials. This practice as a means to access unmarketed Essential Medicines for Neglected Diseases in the US is not totally unique to the CDC. For instance, clofazimine for the treatment of leprosy is only available as an Investigational New Drug as part of an effectively permanent clinical trial run by another government body, the National Hansen's Disease Program (NHDP).⁵⁷¹ Ultimately, however, the fact that decades-old Essential Medicines forming the global standard of care and distributed under the auspices of one of the world's best known public health entities can only be accessed by classifying them as experimental further highlights the incongruity of relying on market forces rather than medical need for formal access.

drugs on the formulary are vaccines and antitoxins for agents that could be used in biological warfare, such as smallpox and anthrax.

⁵⁶⁸ As discussed later in this thesis, both drugs had originally been approved as orphan drugs, underscoring that approval via such pathways does not ensure such drugs remain on the market. Alpern, Jonathan D, Stephen J Dunlop & William M Stauffer. "Broken drug markets in infectious diseases: Opportunities outside the private sector?" (2019) 13:4 PLoS Negl Trop Dis e0007190, online: <<https://dx.plos.org/10.1371/journal.pntd.0007190>>.

⁵⁶⁹ "Hard to Find Antiparasitic Drugs* : Drugs Available from the Parasitic Disease Drug Service" (1974) 120:5 West J Med 391.

⁵⁷⁰ A few drugs supplied by the formulary, such as eflornithine, have technically maintained their licensure, although they are no longer commercially available. CDC Drug Service formulary, online: <<https://www.cdc.gov/laboratory/drugservice/formulary.html>>.

⁵⁷¹ United States Health Resources & Services Administration, "Recommended Treatment Regimens", (April 2018), online: *National Hansen's Disease (Leprosy) Program* <<https://www.hrsa.gov/hansens-disease/diagnosis/recommended-treatment.html>>.

Although some drugs have remained on the CDC Formulary for decades, this is not always a permanent state of affairs. Sometimes they simply disappear entirely. In 2020, for instance, GlaxoSmithKline (GSK) notified the CDC that it was discontinuing production elsewhere in the world of sodium stibogluconate (sold as Pentostam), a decades-old Essential Medicine for leishmaniasis; following the expiration of the last lot of the drug in use, the CDC discontinued its provision.⁵⁷² At the time it was removed, sodium stibogluconate was one of the non-malarial antiparasitic drugs most frequently accessed via the CDC Formulary, accounting for anywhere from 6-22% of all drug releases over the preceding decade.⁵⁷³ Its discontinuation also comes at a time when the Neglected Disease it treats, leishmaniasis, is potentially an emerging health threat in the United States.⁵⁷⁴ GSK did not divest Pentostam to another company; with its withdrawal from the market, it does not appear sodium stibogluconate is formally available in any high-income country. On other occasions, a drug may be brought to market, even decades after its creation, leading it to be removed from the CDC Formulary; the recent example of benznidazole – the only non-malarial antiparasitic accessed more often through the CDC Formulary than sodium stibogluconate – will be explored later on. At the same time, market entry can create its own set of problems, particularly around cost; while attaching any price tag to a drug previously available for free may raise barriers, in some cases market entry in the United States has led to stunningly high price increases. The case of artesunate, which went from being provided for free in the US to costing tens of thousands of dollars for a course of treatment is discussed later in this thesis. However, it was a different mode of exploitation of old drugs that would ultimately draw public attention to off-patent Essential Medicines for Neglected Diseases.

⁵⁷² CDC Drug Service formulary, online:

<<https://www.cdc.gov/laboratory/drugservice/formulary.html>>.

⁵⁷³ Chancey, Rebecca J et al., “770. Otherwise Unavailable Non-Malarial Parasitic Disease Treatment Drugs in the United States: an Update from CDC Parasitic Diseases Drug Service” (2020) 7:Supplement_1 Open Forum Infectious Diseases S429–S430, online:

<https://academic.oup.com/ofid/article/7/Supplement_1/S429/6056806>.

⁵⁷⁴ Curtin, John M & Naomi E Aronson, “Leishmaniasis in the United States: Emerging Issues in a Region of Low Endemicity” (2021) 9:3 Microorganisms 578.

Martin Shkreli and the off-patent trolling of pyrimethamine

The existence of the CDC Formulary shows that for some Essential Medicines for Neglected Diseases, the access problem has manifested as it has in Canada: the drug is absent from the formal market, despite government recognition of the need for access. Indeed, in such cases the American government's response has provided a more overt role for the state in ensuring supply than is currently the case in Canada, with the drug acquired via a government agency, and provided at no cost to patients throughout the country. In other cases, however, the drugs are formally available on the market, but access is impacted by another barrier that has only recently been highlighted as a distinct concern, even if it is less a completely novel phenomenon than an extension of long-running practices: off-patent trolling. To briefly reiterate from the introduction, off-patent trolling is the practice of gaining control over the sole approved source of an old drug with a small but critical market, and then exploiting that monopoly to dramatically raise prices. No patent is necessary to create this *de facto* market monopoly. Intellectual property is not totally irrelevant to off-patent trolling – indeed, the well-known tradename under which the drug was sold by the originator company often factors into the story – but it ceases to become the central issue.

A key reason that off-patent trolling has attracted the attention not only of policymakers but of the general public is that it finally put a villainous face to the largely anonymous issue of corporate decision making around the marketing of old medicines. One particular face has become inexorably linked to off-patent trolling, and indeed to pharmaceutical industry misanthropy more generally. That face belongs to former hedge fund manager turned pharmaceutical company CEO Martin Shkreli. Such is the legacy of his brief tenure in the pharmaceutical industry that today the Lown Institute, an American healthcare thinktank, holds the “Shkreli Awards”, which are given to “perpetrators of the ten most egregious examples of profiteering and dysfunction in health care”.⁵⁷⁵ At the time he entered the limelight in 2015, Shkreli had recently switched gears from short-selling biotech stocks to

⁵⁷⁵ Lown Institute, “Shkreli Awards”, online: <<https://lowninstitute.org/projects/shkreli-awards/>>.

running pharmaceutical companies.⁵⁷⁶ Rather than innovate new drugs, however, his only innovations – first with a company called Retrophin, then with his own company Turing Pharmaceuticals – were outrageous new prices for old drugs. His technique for raising these prices was off-patent trolling; the most notorious exercise of this strategy was for pyrimethamine.⁵⁷⁷

Pyrimethamine was developed in the 1950s, under the tradename Daraprim, by the large pharmaceutical company that today is known, after an elaborate series of mergers and acquisitions, as GlaxoSmithKline (GSK). Repeating a common refrain echoed throughout this thesis, pyrimethamine was one of the drugs that earned its discoverers, Gertrude Elion and George Hitchings, a share of the Nobel Prize in Physiology or Medicine in 1988 for their discoveries of “important principles for drug treatment”.⁵⁷⁸ Originally an antimalarial (indicated both for prevention and treatment), it is also the only US FDA-approved treatment for the parasitic disease toxoplasmosis, which is caused by the protozoan parasite *Toxoplasma gondii*. It appears on the WHO MEML for all three of these indications. In North America, it is primarily of importance for treating toxoplasmosis. While a condition that impacts primarily marginalized populations, toxoplasmosis is widespread, including in HICs; in the US, for example, there are an estimated 1.1 million infections per year.⁵⁷⁹ This high number may be misleading, as in healthy individuals it rarely causes serious health problems; however, it can be very serious indeed in immunocompromised individuals, most prominently persons infected with HIV.⁵⁸⁰ Congenital toxoplasmosis is also a potentially life-threatening

⁵⁷⁶ Barrett, Paul M, “Once a Notorious Short Seller, Martin Shkreli Now Sees a Future in Biotech”, *Bloomberg Business* (17 April 2014), online: <<https://www.bloomberg.com/news/articles/2014-04-17/retrophins-martin-shkreli-the-biotech-short-seller-who-went-long>>.

⁵⁷⁷ Pollack, Andrew. “A Huge Overnight Increase in a Drug’s Price Raises Protests”, *The New York Times* (20 September 2015), online: <<http://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html>>.

⁵⁷⁸ The Nobel Assembly at Karolinska Institutet. “Press Release - The Nobel Prize in Physiology or Medicine 1988”, online: <<https://www.nobelprize.org/prizes/medicine/1988/press-release/>>. The prize was shared with James W. Black for his own unrelated drug discoveries.

⁵⁷⁹ Jones, Jeffrey L, Monica E Parise & Anthony E Fiore, “Neglected parasitic infections in the United States: toxoplasmosis” (2014) 90:5 Am J Trop Med Hyg 794–799.

⁵⁸⁰ Basavaraju, Anuradha. “Toxoplasmosis in HIV infection: An overview” (2016) 6:2 Tropical Parasitology 129–135.

concern.⁵⁸¹ Access to pyrimethamine thus remains important in HICs as well as LMICs well over half a century after it was invented. As such, toxoplasmosis is “considered one of the neglected parasitic infections of the United States, a group of five parasitic diseases that have been targeted by CDC for public health action”.⁵⁸²

The Martin Shkreli saga of pyrimethamine pricing and access sets out a pattern that, with the occasional tweak to specific details, is echoed in many cases of off-patent trolling. First, decades after the original patents had expired, the American pyrimethamine supply had become a *de facto* monopoly, with GSK the only licensed producer. Its market position had been further strengthened in the 21st Century, after Roche discontinued its closest competitor in the antimalarial market, Fansidar (a combination of sulfadoxine and pyrimethamine), in the United States (and Canada).⁵⁸³ There are slightly diverging accounts of precisely what happened next, but they agree in their main points. At some point in the 2000s, GSK decided not to continue selling certain legacy Essential Medicines in some markets. In 2010, GSK offloaded the North American market rights for pyrimethamine, including the tradename Daraprim, to Tower Holdings.⁵⁸⁴ At the time, GSK had been selling the drug for about \$1USD per pill.⁵⁸⁵ Accounts differ as to which of Tower Holdings’ subsidiaries – CorePharma or Amedra Pharmaceuticals – technically held pyrimethamine, though the distinction likely does not matter very much as both ultimately appear to have played a role in subsequent events. As

⁵⁸¹ Wallon, Martine & François Peyron, “Congenital Toxoplasmosis: A Plea for a Neglected Disease” (2018) 7:1 Pathogens E25; Paquet, Caroline, Mark H Yudin & Society of Obstetricians and Gynaecologists of Canada. “Toxoplasmosis in pregnancy: prevention, screening, and treatment” (2013) 35:1 Journal of obstetrics and gynaecology Canada: JOGC = Journal d’obstetrique et gynecologie du Canada: JOGC 78–81.

⁵⁸² US CDC, “Parasites - Toxoplasmosis (Toxoplasma infection)” (20 Nov 2020), online: <<https://www.cdc.gov/parasites/toxoplasmosis/index.html>>.

⁵⁸³ “An unusual business” (2015) 33:11 Nat Biotechnol 1113–1113, online: <<http://www.nature.com/articles/nbt.3409>>. In Canada, Fansidar was first marketed in 1989 and discontinued in 2000. However, as noted earlier, it had been the most-requested “emergency drug” in Canada via the EDRP in the mid-1980s. White, G.F. & M.J. Davis, “Antiparasitic drugs: availability and regulatory requirements for ‘emergency’ supply” (1985) 132:3 Can Med Assoc J 273–274.

⁵⁸⁴ Pollack, Andrew. “A Huge Overnight Increase in a Drug’s Price Raises Protests”, *The New York Times* (20 September 2015), online: <<http://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html>>; “An unusual business” (2015) 33:11 Nat Biotechnol 1113–1113, online: <<http://www.nature.com/articles/nbt.3409>>.

⁵⁸⁵ Luo, Jing, Ameet Sarpatwari & Aaron S Kesselheim, “Regulatory Solutions to the Problem of High Generic Drug Costs” (2015) 2:4 Open Forum Infect Dis ofv179.

noted earlier in this section, barriers to off-patent Essential Medicines for Neglected Diseases have sometimes manifested similarly, and sometimes differently, in Canada and the United States. Up until this point, the pyrimethamine story had unfolded in a similar fashion. The Canadian rights to Daraprim were part of GSK's deal with Tower Holdings in 2010.⁵⁸⁶ After this point, the paths diverge, with Canada's coming to an end. Per Health Canada's Drug Database, Daraprim (pyrimethamine), with an original Canadian market approval date of 1952, was cancelled post-market, on June 1, 2013, by Amedra Pharmaceuticals. As such, the only authorized source of pyrimethamine disappeared from the Canadian market, two years before Martin Shkreli became a household name. The reader who has been following closely throughout the preceding pages will no doubt be stunned to learn that, despite its absence from the formal market, pyrimethamine is still recommended in guidelines for physicians treating toxoplasmosis in Canada.⁵⁸⁷ Furthermore, toxoplasmosis is thought to be underreported and underdiagnosed in Canada, even as its impacts on communities living in poverty, including Indigenous communities, are recognized.⁵⁸⁸

Meanwhile, in the United States, pyrimethamine changed hands once more in 2014, after Impax Laboratories announced a deal to purchase Tower Holdings.⁵⁸⁹ In August of 2015, shortly after that deal was concluded, the rights were transferred yet again, passing from Impax to Turing Pharmaceuticals, where Martin Shkreli was CEO.⁵⁹⁰ Within days of the acquisition, Turing had raised the price per

⁵⁸⁶ "CorePharma signs agreement with GSK to acquire Dexedrine US NDAs", *Pharmaceutical Business Review* (25 October 2010), online: <<https://www.pharmaceutical-business-review.com/news/corepharma-signs-agreement-with-gsk-to-acquire-dexedrine-us-ndas-251010/>>.

⁵⁸⁷ Paquet, Caroline & Mark H Yudin, "No. 285-Toxoplasmosis in Pregnancy: Prevention, Screening, and Treatment" (2018) 40:8 *Journal of Obstetrics and Gynaecology Canada* e687–e693, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1701216318304997>>.

⁵⁸⁸ Zeng, Wu et al., "Toxoplasmosis and Toxocariasis: An Assessment of Human Immunodeficiency Virus Comorbidity and Health-Care Costs in Canada" (2016) 95:1 *The American Journal of Tropical Medicine and Hygiene* 168–174, online: <<https://ajtmh.org/doi/10.4269/ajtmh.15-0729>>.

⁵⁸⁹ Impax Laboratories Inc, "Press Release - Impax To Acquire Tower Holdings, Inc. And Lineage Therapeutics Inc.", (9 October 2014), online: <<https://www.prnewswire.com/news-releases/impax-to-acquire-tower-holdings-inc-and-lineage-therapeutics-inc-278627101.html>>.

⁵⁹⁰ PRNewswire, "Press Release - Impax Announces Sale of Daraprim® to Turing Pharmaceuticals AG", (10 August 2015), online:

tablet from what had by this time become \$13.50 to \$750USD.⁵⁹¹ Almost immediately, the pyrimethamine story hit the headlines. While it was not the only off-patent drug to be trolled around this time – indeed, the near-simultaneous reports of the price increase on cycloserine by Rodelis Therapeutics helped to raise awareness of grotesque price increases and the phenomenon of off-patent trolling of Essential Medicines – Shkreli himself helped ensure that once he made the headlines, he stayed there.⁵⁹²

Quickly and widely dubbed “the pharma bro” for his obnoxious fratboyish persona, Shkreli rapidly cemented his status as the face of greedy pharmaceutical executives.⁵⁹³ In turn, an adjective regularly applied to that face was “punchable”; this descriptor of Martin Shkreli became sufficiently part of the zeitgeist, in articles like “The 9 Most Punchable Martin Shkreli Faces (Just From Today)” and “We Asked Scientists: Just How Punchable Is Martin Shkreli’s Face?” that it served to teach many people (including this author) the useful German word *backpfeifengesicht* (per Google Translate: “a face in need of a fist”).⁵⁹⁴ As the months progressed, bizarre antics, such as paying an exorbitant amount of money for the sole copy of an album by hip-hop group the Wu-Tang Clan (and then engaging in an online feud with one of its members), or offering his online followers money for a lock of Hilary Clinton’s hair, would cement his supervillain

<<https://web.archive.org/web/20150925060719/http://www.prnewswire.com/news-releases/impax-announces-sale-of-daraprim-to-turing-pharmaceuticals-ag-300125865.html>>.

⁵⁹¹ Pollack, Andrew. “A Huge Overnight Increase in a Drug’s Price Raises Protests”, *The New York Times* (20 September 2015), online: <<http://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html>>.

⁵⁹² Pollack, Andrew, “Drug Goes From \$13.50 a Tablet to \$750, Overnight”, *The New York Times* (20 September 2015), online: <<https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html>>.

⁵⁹³ The precise origins of his christening as such are unclear, but the term was being used in headlines in major newspapers by late September 2015. See e.g., Miller, Michael E, “‘Pharma bro’ Martin Shkreli and the very American debate over maximizing profit”, *Washington Post* (23 September 2015), online: <<https://www.washingtonpost.com/news/morning-mix/wp/2015/09/23/pharma-bro-martin-shkreli-and-the-very-american-debate-over-maximizing-profit/>>.

⁵⁹⁴ Goldstein, Jessica M. “We Asked Scientists: Just How Punchable Is Martin Shkreli’s Face?”, *ThinkProgress* (10 February 2016), online: <<https://archive.thinkprogress.org/we-asked-scientists-just-how-punchable-is-martin-shkreli-s-face-b460e544d3ee/>>; Wing, Nick. “The 9 Most Punchable Martin Shkreli Faces (Just From Today)”, *Huffington Post US* (4 February 2016), online: <https://www.huffingtonpost.ca/entry/martin-shkreli-faces_n_56b388d7e4b01d80b2456139>.

celebrity status, even as the precise details of what exactly he had done to pyrimethamine, and how to address it, were increasingly lost in the shuffle.⁵⁹⁵

As a consequence not merely of his actions but his wider pop-cultural status, Shkreli became so indelibly associated with abhorrent pharmaceutical company practices that even those who should know better misrepresented his actions, and the underlying problems they demonstrated. For instance, one impassioned commentary by an American law professor states that the “headline-producing greed of ‘pharma bro’ Martin Shkreli was just the most dramatic example of a pharmaceutical industry whose patent monopolies grant it immunity from market forces while its political clout shields it from government regulation”.⁵⁹⁶ While anger at Shkreli for abusing monopolies is justified, framing that links monopolies exclusively with patent rights risks further conflating access to medicines with intellectual property barriers, rather than treating the latter as just one factor affecting the former, a distinction this thesis has consistently emphasized. Nonetheless, with Shkreli’s notoriety transcending borders, such conflations occurred in other countries as well. For instance, speaking to the Economic Club of Canada in 2017, Canada’s Minister of Health Jane Philpott referred to Shkreli by name and said “We don’t have situations like that in Canada, because of some of the protections I’ll discuss today”.⁵⁹⁷ However, while her speech does go on to discuss measures to address high prices for patented medicines, including announcing proposed reforms to the Patented Medicine Prices Review Board (PMPRB), she

⁵⁹⁵ Leonard, Devin & Annmarie Hordern, “Who bought the most expensive album ever made?”, *Bloomberg Businessweek* (9 December 2015), online: <<https://www.bloomberg.com/features/2015-martin-shkreli-wu-tang-clan-album/>>; Andrews, Travis M, “‘Pharma bro’ Martin Shkreli at war with Ghostface Killah after rapper insults his nose”, *The Washington Post* (29 January 2016), online: <<https://www.washingtonpost.com/news/morning-mix/wp/2016/01/29/pharma-bro-martin-shkreli-at-war-with-ghostface-killah-after-rapper-insults-his-nose/>>; Pierson, Brendan, “Shkreli ordered jailed after online bounty on Hillary Clinton’s hair”, *Reuters* (20 September 2017), online: <<https://www.reuters.com/article/legal-usa-crime-shkreli-idUSKCN1BP2ES>>.

⁵⁹⁶ Quigley, Fran. “Disgusted With Sky-High Drug Prices, California Voters Take On Big Pharma”, *Truthout* (18 August 2016), online: <<https://truthout.org/articles/disgusted-with-sky-high-drug-prices-california-voters-take-on-big-pharma/>>.

⁵⁹⁷ Philpott, Jane, *Remarks from the Honourable Jane Philpott, Minister of Health, to the Economic Club of Canada – May 16, 2017* (Economic Club of Canada, 2017), online: <https://www.canada.ca/en/health-canada/news/2017/05/economic_club_ofcanada-may162017.html>.

never discusses any protections that would actually prevent a price hike on an off-patent drug, or that would have ensured pyrimethamine remained on the Canadian market.⁵⁹⁸ This is because there are no such federal measures in place. Perhaps more importantly, her speech never acknowledges pyrimethamine's total absence from the Canadian market.

A crucial element that must be emphasized before continuing is that the core element of off-patent trolling is, on its own, completely legal in the United States. Broadly speaking, while competitors who conspire to mutually raise prices might be breaking the law, monopolies are allowed to unilaterally exert monopoly powers over their own pricing. This is true even where those price increases could have serious repercussions for access to a lifesaving medication. A similar approach to competition has been taken by the Canadian government.⁵⁹⁹ Thus, while Martin Shkreli ultimately did go to jail, where he remains at the time of this writing, it was for securities fraud, not for the price gouging that brought him into the public eye.⁶⁰⁰

Some of these charges related to his time with his initial company, Retrophin. While securities fraud is outside the ambit of this thesis, some of his other activities at Retrophin are highly relevant, including for illustrating parallels

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⁵⁹⁸ She also talks about bulk purchasing power, which is not irrelevant to drug pricing, but less applicable to small market drugs, and even less so to the SAP. Philpott, Jane, *Remarks from the Honourable Jane Philpott, Minister of Health, to the Economic Club of Canada – May 16, 2017* (Economic Club of Canada, 2017), online: <https://www.canada.ca/en/health-canada/news/2017/05/economic_club_ofcanada-may162017.html>.

⁵⁹⁹ This Canadian stance is spelled out in a 2018 submission to the OECD on the topic of excessive pharmaceutical pricing: "The *Competition Act* does not contain a prohibition against excessive pricing. Consequently, the Bureau's advocacy and enforcement work focuses on protecting the competitive process rather than enforcing a particular market outcome. In other words, the Bureau's work targets the disease (lack of competition) rather than the symptom (excessive prices). This approach ensures that the Bureau is not required to engage in price regulation, which is at odds with traditional Canadian competition law principles". Competition Bureau Canada, "Competition Bureau Submission to the OECD on Excessive Pricing in Pharmaceuticals", (5 November 2018), online: <<https://www.competitionbureau.gc.ca/eic/site/cb-bc.nsf/eng/04426.html>>. Most provinces do have price-gouging provisions under their consumer protection legislation; however, these have yet to play a major role in pharmaceutical pricing.

⁶⁰⁰ Subsequent legal action relating to particular facets of his off-patent trolling will be addressed later. Walters, Joanna, "Martin Shkreli found guilty of fraud by jury in New York", *The Guardian* (4 August 2017), online: <<https://www.theguardian.com/us-news/2017/aug/04/martin-shkreli-guilty-securities-fraud-new-york>>; Romo, Vanessa, "Martin Shkreli Sentenced To 7 Years For Securities Fraud", *NPR* (9 March 2018), online: <<https://www.npr.org/sections/thetwo-way/2018/03/09/592368883/martin-shkreli-sentenced-to-seven-years-for-securities-fraud>>.

between drugs for Neglected Diseases and those for Rare Diseases. It was while at Retrophin that Shkreli piloted his off-patent trolling strategy, a year before pyrimethamine hit the headlines, by similarly gaining sole market rights to Thiola (tiopronin), an off-patent drug for the rare disease cystinuria, and raising the price from \$1.50USD per pill to \$30.⁶⁰¹ While his pre-pyrimethamine trolling of tiopronin stayed comparatively under the radar – perhaps surprisingly, given that Rare Diseases generally attract more attention than Neglected Diseases in the US, much as they do in Canada – prominent pharma industry commentator Derek Lowe called it “the most unconscionable drug price hike I have yet seen”.⁶⁰² Lowe made this statement even before evidence emerged that Shkreli himself had “wanted to take a price increase of some four times that amount, but was stopped by others at Retrophin who considered such a large increase unwise or unconscionable”.⁶⁰³

One of the reasons Lowe makes this assessment is that in the case of tiopronin, as with pyrimethamine, Shkreli was demonstrating one of the hallmarks of off-patent trolling: the price hike is not justified by even the pretence of further research. Broadly speaking, it is not an unusual practice for pharmaceutical companies to tweak the formulations of lucrative existing drugs, or find new indications for those drugs, in order to receive new legal exclusivities (patents and otherwise). This thesis will not delve deeply into the controversies surrounding patent evergreening and similar practices.⁶⁰⁴ However, earning incentives, such as a patent, that are intended to encourage research and development generally requires that at least some minimal effort is expended; furthermore, that effort ostensibly results in at least some marginal benefit to the patient or increase in

⁶⁰¹ Ramsey, Lydia, “The CEO who jacked up the price of a drug by 5,000% has done this before”, *Business Insider* (23 September 2015), online: <<https://www.businessinsider.com/martin-shkreli-history-of-price-hikes-2015-9>>.

⁶⁰² Lowe, Derek, “The Most Unconscionable Drug Price Hike I Have Yet Seen”, (11 September 2014), *In the Pipeline* (blog), online: <https://blogs.sciencemag.org/pipeline/archives/2014/09/11/the_most_unconscionable_drug_price_hike_i_have_yet_seen>.

⁶⁰³ United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System* (United States Senate, 2016).

⁶⁰⁴ But see e.g., Roehr, Bob, “Ban evergreening and restricting generics to reduce drug prices, says US academy” (2017) *BMJ* j5624, online: <<https://www.bmj.com/lookup/doi/10.1136/bmj.j5624>>; Collier, Roger, “Drug patents: the evergreening problem” (2013) 185:9 *CMAJ* E385-386.

scientific knowledge, even if that benefit does not justify the magnitude of the reward received. While such mechanisms rewarding innovation can be exploited, off-patent trolling takes exploitation a step further in that it does not carry even a patina of justification. It is total free riding on a pre-existing natural monopoly.

Unsurprisingly, Shkreli's attempts to justify these extreme price hikes in the media fell flat. When confronted, Shkreli's explanation for the price hike on pyrimethamine was that the proceeds were needed in order to develop better treatments for toxoplasmosis. "There are very few people who care about toxoplasmosis more than me," he told *The Guardian* in 2015; "I think I know more about toxoplasmosis than anyone in the world".⁶⁰⁵ Although Shkreli's subsequent legal troubles seem to have put an end to this purported quest for a novel toxoplasmosis treatment, there is little tangible evidence that any such efforts had been embarked upon in the first place.⁶⁰⁶ By contrast, one of Shkreli's emails describes the pyrimethamine plan as follows, highlighting both the price hike and the belief that barriers to market entry would slow any competition for a number of years:

I think it will be huge. We raised the price from \$1,700 per bottle to \$75,000. Previously Impax sold 10,000 bottles per annum (50% is given away, however). So 5,000 paying bottles at the new price is \$375,000,000—almost all of it is profit and I think we will get 3 years of that or more. Should be a very handsome investment for all of us. Let's all cross our fingers that the estimates are accurate.⁶⁰⁷

Thus, in pursuit of unearned profits, Shkreli was personally exacerbating both sides of the issue by exploiting the unmet need for research into new drugs for Neglected

⁶⁰⁵ Walters, Joanna, "Turing boss Martin Shkreli says Daraprim price drop 'might curtail research for lethal diseases'", *The Guardian* (24 September 2015), online: <[Turing boss Martin Shkreli says Daraprim price drop 'might curtail research for lethal diseases'](#)>.

⁶⁰⁶ At the very least, no clinical trials were registered with any credible authority, and no peer-reviewed publications exist in support of this claim.

⁶⁰⁷ United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System*, (United States Senate, 2016).

Diseases in order to justify decreasing affordable access to an Essential Medicine that already exists. Furthermore, in order to do so he was relying in part on the inefficiencies and obstacles of the existing pharmaceutical regulatory system to protect him from competition, at least in the short term.

Nevertheless, while indelibly associated with the practice, Shkreli cannot take full credit (or blame) for the idea of off-patent trolling. Price hikes on old medicines are certainly not new. A study from the US Government Accountability Office (GAO), which found that more than “300 of the 1,441 established generic drugs analyzed had at least one extraordinary price increase of 100 percent or more between first quarter 2010 and first quarter 2015”, reinforces the notion that similar pricing practices, if not always to the extremes of Martin Shkreli, had been happening for some time before pyrimethamine hit the headlines.⁶⁰⁸ In fact, these increases had been such that over this time period, the GAO “found that drugs with extraordinary price increases moderated the overall decline in generic drug prices” in the United States.⁶⁰⁹ As such, Shkreli was less the innovator than the brash messenger who would bring off-patent trolling into the public eye.

Furthermore, those engaged in off-patent trolling also transcended borders; while both pyrimethamine and cycloserine had already disappeared from the Canadian market before either drug attracted the attention of trolls, the Canadian-based company Valeant Pharmaceuticals, headquartered in Laval QC, also engaged in the practice with gusto.⁶¹⁰ Previously based in the USA, Valeant relocated its headquarters to Canada after a merger with the Canadian company Biovail in 2010.⁶¹¹ This border hopping meant that much of its focus remained on the American market. In February of 2015, some months before Martin Shkreli became a household name, Valeant acquired the American rights to the blood-pressure

⁶⁰⁸ United States Government Accountability Office, *Generic Drugs Under Medicare Part D Generic Drug Prices Declined Overall, but Some Had Extraordinary Price Increases*, GAO-16-706 (2016).

⁶⁰⁹ United States Government Accountability Office, *Generic Drugs Under Medicare Part D Generic Drug Prices Declined Overall, but Some Had Extraordinary Price Increases*, GAO-16-706 (2016).

⁶¹⁰ Valeant has since changed names. Following the off-patent trolling controversy discussed in these pages, it has now been rebranded as Bausch Health Companies Inc.

⁶¹¹ Jordan, Pav & Esha Dey, “Drugmaker Biovail to buy Valeant in \$3.3 billion deal”, *Reuters* (21 June 2010), online: <<http://www.reuters.com/article/2010/06/21/us-biovail-valeant-idUSTRE65K1LA20100621>>.

drug Nitropress (sodium nitroprusside, an Essential Medicine) and the heart-rhythm treatment Isuprel (isoprenaline or isoproterenol). That same day, it tripled the price of Nitropress and raised the price of Isuprel more than sixfold.⁶¹² In both cases, the Canadian market was served by other companies, meaning the effects were restricted to the United States. However, Canada would feel the effects of Valeant's considerably more extreme price increase for trientine (sold as Syprine), a treatment for the Rare Disease Wilson's disease.⁶¹³ As explored in more detail elsewhere in this thesis, trientine did not have market approval in Canada, and thus was only available via the SAP. At the same time that Valeant raised its American price from \$800 per 100 tablets to roughly \$11,000 for 100 tablets, it also stopped providing it for free to Canadian patients, leaving them to pay the new American price as well.⁶¹⁴

A further example of the impact of Valeant's actions involves another Essential Medicine that, like pyrimethamine, is of particular relevance in HICs for an opportunistic infection in persons with HIV, in this case cryptococcal meningitis.⁶¹⁵ Flucytosine was developed in 1957 and initially marketed by Roche;

⁶¹² Rockoff, Jonathan D. "Bernie Sanders, Elijah Cummings Question Valeant on Heart-Drug Price Increases", *The Wall Street Journal* (14 August 2015), online: <<http://www.wsj.com/articles/bernie-sanders-elijah-cummings-question-valeant-on-heart-drug-price-increases-1439574723>>.

⁶¹³ As revisited later, the trientine saga follows a similar pattern to other drugs in this section. Long sold inexpensively by Merck, it was divested to Aton Pharma in 2006; Aton raised prices and was in turn acquired by Valeant in 2010. See Roberts, Eve A, Matthew Herder & Aidan Hollis. "Fair pricing of 'old' orphan drugs: considerations for Canada's orphan drug policy" (2015) 187:6 CMAJ 422-425, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.140308>>.

⁶¹⁴ Chandok, Natasha & Eve A Roberts, "The Trientine Crisis in Canada: A Call to Advocacy" (2014) 28:4 Canadian Journal of Gastroenterology and Hepatology 184-184, online: <<http://www.hindawi.com/journals/cjgh/2014/672809/>>. It is worth noting that trientine finally received Health Canada approval – and not via Valeant – in 2020, a story revisited later.

⁶¹⁵ Molloy, Síle F et al., "Cryptococcal meningitis: A neglected NTD?" (2017) 11:6 PLoS Negl Trop Dis e0005575, online: <<https://dx.plos.org/10.1371/journal.pntd.0005575>>. It should be noted that, unlike many of the other drugs discussed in this thesis, this particular off-patent Essential Medicine for a Neglected Disease has not been widely available in LMICs either, in some instances because it was never brought to market or, in cases like South Africa, it was discontinued. Govender, Nelesh Premapragasan, Graeme Meintjes & Shabir Bano, "Access to flucytosine for HIV-infected patients with cryptococcal meningitis - an urgent need" (2014) 104:9 S Afr Med J 594, online: <<http://www.samj.org.za/index.php/samj/article/view/8713>>. In turn, cryptococcal meningitis remains a major cause of HIV-related deaths worldwide. Loyse, Angela et al., "Cryptococcal meningitis: improving access to essential antifungal medicines in resource-poor countries" (2013) 13:7 Lancet Infect Dis 629-637. This is also another instance where treatment choices may be guided by pharma company donations of another Essential Medicine (fluconazole) instead. See e.g.,

by 2015, thanks to its acquisition by Valeant, the US price was approximately 9000% that in the UK.⁶¹⁶ Interestingly, although Health Canada's drug database indicates flucytosine has never been marketed in Canada, the FDA drug database confirms that Ancobon, the flucytosine product marketed by Valeant in the United States, was actually manufactured in Manitoba.⁶¹⁷ These examples illustrate how the American phenomenon of off-patent trolling both implicated Canadian companies, and affected Canadian patients.

For all the attention off-patent trolling has attracted, however, it must be kept in mind that it is merely another symptom of the underlying problem affecting sustainable access to important off-patent drugs. As outlined earlier, small markets for inexpensive old drugs are not a particularly appealing prospect for commercial manufacturers, even when there are no patents to inhibit market entry. These are drugs that any company could make and sell in theory, but few if any are interested in selling in practice. What off-patent trolling does is to tweak this formula by abruptly assigning a very different commercial value to the product, something it is able to do precisely because of the medical importance of the drug to the patients who need it.

One version of this formula was spelled out by the United States Senate Special Commission on Aging (Special Commission) in the wake of Shkreli's exploits and other high-profile incidents of off-patent trolling. Four of the companies mentioned thus far formed the central focus of the Special Commission's examination: Shkreli's previous company Retrophin (for tiopronin) and his current company Turing (for pyrimethamine); Québec's Valeant (for sodium nitroprusside, isoproterenol, trientine and another Essential Medicine, penicillamine, which is used to treat the same Rare Disease as trientine); and

Shroufi, Amir et al., "Time to embrace access programmes for medicines: lessons from the South African flucytosine access programme" (2020) 95 *International Journal of Infectious Diseases* 459–461, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1201971220301168>>.

⁶¹⁶ Merry, Matthew & David R Boulware, "Cryptococcal Meningitis Treatment Strategies Affected by the Explosive Cost of Flucytosine in the United States: A Cost-effectiveness Analysis" (2016) 62:12 *Clin Infect Dis* 1564–1568.

⁶¹⁷ This remains true even now that Valeant has been rechristened Bausch Health.

Rodelis (cycloserine).⁶¹⁸ It is worth reiterating once again that the majority of the drugs drawing the particular scrutiny of the Special Commission were by this point entirely absent from the Canadian market; the Neglected Disease drugs pyrimethamine and cycloserine had been discontinued, and the Rare Disease drugs tiopronin and trientine never introduced. The absence of these drugs from the Canadian market has never attracted the same political attention in Canada as their price increases did in America.

The Special Commission's resulting 2016 report identified five common traits [*italicized*] of drugs vulnerable to off-patent trolling. This list is itself incomplete; for instance, the fact off-patent trolling piggybacks on existing drugs without even the cursory tweaks that drive other exploitative practices like patent evergreening certainly deserves to be acknowledged as a key trait. Nonetheless, the Special Commission's list offers some useful guidance. The first trait is that the drug is a *sole-source* drug with only one approved manufacturer. This provides monopoly power over pricing, and a window without competition before any competitor can enter the market given the time and resources necessary to do so. Here, the regulatory system can actually serve to protect the trolling party; a company with no history in the pharmaceutical business can acquire an existing sole source and raise prices immediately, while a potential competitor with decades of experience making the same drug in foreign markets would have to go through the market approval process.

The second is that the drug is the *gold standard* for treatment – the best available drug, thus ensuring doctors would continue to prescribe the medicine rather than shift to alternatives (provided such alternatives exist at all, and are in turn themselves available). Here, the parallels with the broader concept of Essential Medicines are clear, even for drugs not themselves found on the WHO MEML. Holding both such treatments for a single condition – as Valeant did with trientine and penicillamine for Wilson's disease – compounds the leverage for

⁶¹⁸ United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System* (United States Senate, 2016). Penicillamine is discussed in more detail later in this thesis.

trolling. The third is that the drug serves a *small market* that is not attractive to competitors; quite disturbingly, the Special Commission also found small market drugs “provided another attractive advantage—the patient population dependent upon them would be too small to organize an effective opposition to the price increase”.⁶¹⁹ The fourth trait identified by the Special Commission is that the drug is made available by *closed distribution*, where the company exerts additional control over access, such as supplying it via a closed distribution system or specialty pharmacy, which further inhibits competition by making it harder for potential competitors to obtain necessary samples to use as comparators in their own applications for market entry. It is not clear this fourth trait is truly a necessary and defining one rather than simply an aggravating factor; that said, as will be revisited shortly, it is the trait that yielded the only potential pathway for direct legal action against the perpetrators. The last feature, by contrast, is unquestionably a key trait of off-patent trolling: *price-gouging*.⁶²⁰

As the reader may have deduced, the same characteristics that make Essential Medicines for Neglected Diseases vulnerable to being discontinued or simply never introduced in markets with a small pool of patients also make them vulnerable to off-patent trolling. In 2016, in the wake of the Shkreli media storm, Alpern and colleagues identified ten off-patent Essential Medicines that had undergone price increases in the United States ranging from 212% to 5433% in recent years, including five for Neglected Diseases.⁶²¹ Interestingly, of the five Neglected Disease drugs identified, only one (praziquantel) is marketed in Canada, while all five of the non-Neglected Disease drugs are available.⁶²² They then

⁶¹⁹ United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System* (United States Senate, 2016).

⁶²⁰ United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System*, (United States Senate, 2016).

⁶²¹ Alpern, Jonathan D, John Song & William M Stauffer. “Essential Medicines in the United States — Why Access Is Diminishing” (2016) 374:20 N Engl J Med 1904–1907, online: <<http://www.nejm.org/doi/10.1056/NEJMp1601559>>.

⁶²² The five identified for Neglected Diseases are cycloserine, pyrimethamine, albendazole, flucytosine, and praziquantel. The remaining five consist of penicillamine and sodium nitroprusside,

identified other medicines found on the WHO MEML that shared similar characteristics in the US, including having a single source or small number of sources of supply, and serving a small but crucial market. Of the 16 drugs they identified as being at risk, all are used to treat Neglected Diseases.⁶²³ The authors list seven of them for the treatment of tuberculosis.⁶²⁴ The rest are all treatments for other Neglected Diseases, including Hansen's disease (leprosy), strongyloidiasis, malaria, and Chagas disease.⁶²⁵ Just as a sizeable majority of previously trolled drugs for Neglected Diseases were already absent from the Canadian market, less than half of the drugs Alpern and colleagues identified as being at risk of future exploitation in the United States are currently available in Canada.⁶²⁶

When it comes to the market presence of such drugs, the Canada/US divide illustrates the knife-edge on which some of these drugs seem to rest. In Canada, business decisions led to pyrimethamine and cycloserine being discontinued, and others not being brought to market in the first place. By contrast, in the US, such drugs have exhibited the remarkably consistent phenomenon of being transferred to other companies, often repeatedly, rather than discontinued, until trolling finally occurred. This suggests some recognition by multiple parties that these Essential

both previously discussed in the context of Valeant, and three cancer drugs, chlorambucil, procarbazine, and dactinomycin.

⁶²³ Quinidine gluconate (IV), rifapentine, rifabutin, pyrazinamide, capreomycin, streptomycin, aminosalicic acid, ethionamide, pentamidine (IV & inhaled), sulfadiazine, ivermectin, clofazimine, dapson, paromomycin, benznidazole and permethrin (cream). Alpern, Jonathan D, John Song & William M Stauffer. "Essential Medicines in the United States — Why Access Is Diminishing" (2016) 374:20 N Engl J Med 1904–1907, online: <<http://www.nejm.org/doi/10.1056/NEJMp1601559>>. There are a few caveats that should be made to this list, however; First, while quinidine gluconate can be used for malaria, that indication has never appeared on the WHO MEML; furthermore, it was removed from the WHO MEML for its only listed indication, cardiac arrhythmia, in 2009. At the same time, use for malaria also highlights the issue of off-label usage made possible by formal availability. Second, the list includes clofazimine, which was approved as an orphan drug in the United States, but discontinued by the time of this article, and benznidazole, which had not yet been formally approved, making their inclusion somewhat confusing, though as will be seen later on, benznidazole would indeed be at a risk of a major price increase via other means.

⁶²⁴ Today, that number would be eight. Clofazimine, identified by the authors for leprosy, is also used for DR-TB, an indication added to the WHO MEML after the article was published.

⁶²⁵ Alpern, Jonathan D, John Song & William M Stauffer. "Essential Medicines in the United States — Why Access Is Diminishing" (2016) 374:20 N Engl J Med 1904–1907, online: <<http://www.nejm.org/doi/10.1056/NEJMp1601559>>.

⁶²⁶ At the time the article was published, 10/16 were not marketed in Canada; ivermectin has, as discussed elsewhere, since come to market.

Medicines have value, but also an unwillingness to maintain the status quo and an inability to appropriately capitalize upon that value in a way that maintains affordable patient access. Supporting this notion is evidence that transfers of the market rights to off-patent drugs are often followed by price increases. For instance, one American study found that among “FDA-approved, off-patent brand-name drugs in tablet or capsule formulation and in monopolies or duopolies, more than half were acquired since 2000, with their median price more than doubling after acquisition”.⁶²⁷ It is unsurprising that drugs whose rights change hands would be more prone to price increases; after all, companies purchase drugs as an investment of some kind. Raising the price is one obvious way to capitalize on (or at least recoup) that investment; by extension, it should also come as no shock when a drug changing hands multiple times also undergoes multiple price increases. What Shkreli and other off-patent trolls did was not to invent this approach, but to display particular audacity in how high, and how quickly, the price was raised. As Tallapragada puts it, this was a new economic calculation:

What Turing, Valeant, Rodelis, and others share is the view that many off-patent drugs are undervalued assets, at least relative to prices that insurers and patients with no therapeutic alternatives are willing to pay. By this logic the original owners of these off-patent drugs underpriced their products because they lacked the profit motive to charge more, as in the case of Purdue and cycloserine, or they neglected them in favor of more lucrative drugs in their product portfolio, as in the case of GlaxoSmithKline, the longtime manufacturer of Daraprim.⁶²⁸

In this context, the value placed on drugs that the originator company would be willing to divest from, or even simply discontinue, can seem surprising at first

⁶²⁷ Gupta, Ravi et al. “The Impact of Off-Patent Drug Acquisitions on Prices” (2018) 33:7 Journal of General Internal Medicine 1007–1009, online: <<http://link.springer.com/10.1007/s11606-018-4372-3>>.

⁶²⁸ Tallapragada, Naren P. “Off-patent drugs at brand-name prices: a puzzle for policymakers” (2016) 3:1 J Law and the BioSci 238–247, online: <<https://academic.oup.com/jlb/article-lookup/doi/10.1093/jlb/lsw008>>.

glance. Turing paid \$55 million USD for the US rights to pyrimethamine.⁶²⁹ These rights, to reiterate, included no patent rights (though they did include the tradename Daraprim). On the one hand, this is considerably cheaper than the cost of developing a new, innovative drug, even at the lower end of a rather contentious spectrum (recent estimates of the mean cost of developing a novel drug have ranged anywhere from \$314 million to \$2.8 billion USD).⁶³⁰ On the other, had Turing's goal been simply to sell pyrimethamine, it could have entered the market with its own generic version of the product for far less money; an Abbreviated New Drug Application (ANDA) – analogous to the Canadian ANDS – currently costs less than \$200,000 in the United States.⁶³¹ That they did not further underscores that the *de facto* monopoly was a big part of the attraction.

As the US Senate Commission concluded, the price hike on trolled drugs was intended to maximally exploit the market before competitors could enter the market and bring the price back down. At the same time, however, the Daraprim story also shows that a multimillion-dollar market already existed at a pre-trolled price; the year before Turing acquired the rights, US sales of Daraprim had been just under \$10 million for just over 8,800 prescriptions.⁶³² This suggests the American pyrimethamine market may be an entirely viable one, just an insufficiently profitable one for most potential producers. Nevertheless, pricing is a double-edged sword for access. At a high price the drug may be too expensive to be affordable, but at too low a price it might not stay on the market at all; as Alpern and colleagues highlight, “While these drugs are at risk for exploitative pricing strategies...the lack of generic competition in this space and the small market suggests that drug discontinuation and withdrawal from the market is another

⁶²⁹ “Impax sells US Daraprim rights to Turing Pharma”, (10 August 2015), online: *The Pharma Letter* <<https://www.thepharmaletter.com/article/impax-sells-us-daraprim-rights-to-turing-pharma>>.

⁶³⁰ Wouters, Olivier J, Martin McKee & Jeroen Luyten, “Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018” (2020) 323:9 JAMA 844, online: <<https://jamanetwork.com/journals/jama/fullarticle/2762311>>.

⁶³¹ This number fluctuates year-to-year, but not so much as to fundamentally alter this point. US FDA, “Generic Drug User Fee Amendments” (10 February 2021), online: <<https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments>>.

⁶³² Pollack, Andrew, “Drug Goes From \$13.50 a Tablet to \$750, Overnight”, *The New York Times* (20 September 2015), online: <<https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html>>.

risk”.⁶³³ Indeed, this has come to pass since the article was written, as two of the drugs identified as being at risk of trolling, capreomycin and quinidine gluconate (IV), have instead been discontinued in the US.⁶³⁴

Ultimately, protecting his new investment may have proven to be the fatal overreach for Shkreli; while the initial price hike on its own broke no laws, subsequent measures to prevent market entry by new competitors fell afoul of antitrust authorities. This is where the least essential of the Special Commission’s traits of off-patent trolling, *closed distribution*, takes centre stage. In January of 2020, Shkreli, along with Turing (by this point rechristened Vyera, and wholly owned by a Phoenixus AG, a Swiss corporation set up by Shkreli) were sued by New York’s Attorney General and the Federal Trade Commission.⁶³⁵ According to the complaint, the alleged anticompetitive actions include using a “complex web of contractual restrictions” to restrict the resale of Daraprim to generics companies, restricting access to necessary ingredients, and signing “data-blocking” arrangements with distributors to prevent sales data from being provided to third-party data reporting companies.⁶³⁶ Vyera (Turing) ultimately settled with the FTC.⁶³⁷ Shkreli himself, however, was ordered to disgorge \$64.6 million in net

⁶³³ Alpern, Jonathan D, Stephen J Dunlop & William M Stauffer. “Broken drug markets in infectious diseases: Opportunities outside the private sector?” (2019) 13:4 PLoS Negl Trop Dis e0007190, online: <<https://dx.plos.org/10.1371/journal.pntd.0007190>>.

⁶³⁴ Interestingly, neither of these drugs were still on the WHO MEML by the time of discontinuation. The circumstances of capreomycin, removed from both international treatment guidelines and the WHO MEML, will be revisited shortly. Nevertheless, the US CDC considered quinidine’s discontinuation sufficiently important in relation to the treatment of severe malaria that they put out a notice about it. US Centers for Disease Prevention and Control, “Quinidine Availability in the United States”, (14 December 2017), online: <https://www.cdc.gov/malaria/new_info/2017/Quinidine_2017.html>.

⁶³⁵ Forkin, Jim & Dan Mangan, “Federal Trade Commission, New York Attorney General seek lifetime ban for ‘Pharma bro’ Martin Shkreli for ‘illegally monopolizing’ drug”, *CNBC News* (27 January 2020), online: <<https://www.cnn.com/2020/01/27/martin-shkreli-sued-by-ftc-for-daraprim-monopoly.html>>.

⁶³⁶ *Federal Trade Commission State of New York v. Vyera Pharmaceuticals, LLC, Phoenixus AG, Martin Shkreli and Kevin Mulleady - Complaint for Injunctive and Other Equitable Relief* (2020), paras 4-7.

⁶³⁷ Bartz, Diane & Jonathan Stempel, “U.S. FTC settles with Vyera over Daraprim, Shkreli trial still on”, *Reuters* (7 December 2021), online: <<https://www.reuters.com/business/healthcare-pharmaceuticals/ftc-settles-with-vyera-over-daraprim-shkreli-litigation-go-2021-12-07>>.

profits from his wrongdoing, and barred for life from the pharmaceutical industry.⁶³⁸

It is ironic that Shkreli's actions around closed distribution, which were intended merely to protect the underlying act of trolling, turned out to be the only direct avenue of legal redress. Meanwhile, the larger pattern of less-extreme price increases on single-source off-patent drugs in the United States, including multiple Essential Medicines for Neglected Diseases, remains mostly unaffected.⁶³⁹ More broadly, the conditions that permitted off-patent trolling to occur, and those that have impacted the market status of off-patent Essential Medicines for Neglected Diseases in general, remain largely untouched. Slapping a lifetime ban from the pharmaceutical industry on Martin Shkreli might feel good, but it does not address these underlying systemic problems.

Commented [AH2]: Medicare bill?

Divestment and the Road to Off-Patent Trolling

Boiled down to its essentials, off-patent trolling is simple: control the only source of an old drug, and then jack up the price. However, the story of how and why an Essential Medicine finds itself in the hands of someone like Martin Shkreli has been a more complicated one. To understand the malady of off-patent trolling, it is necessary to follow it upstream to its source. After all, by definition off-patent trolling does not involve the creation of a new drug. An Essential Medicine must, however, originate somewhere. This part of the story thus begins with the companies that did, once upon a time, develop a novel drug that was of such medical importance that it became an Essential Medicine.

The pattern for off-patent trolling has consistently unfolded in a similar manner, as exemplified by the pyrimethamine example. First, the innovator company decides it no longer wishes to market its legacy Essential Medicine. Here,

⁶³⁸ *Federal Trade Commission, State of New York, State of California, State of Ohio, Commonwealth of Pennsylvania, State of Illinois, State of North Carolina, & Commonwealth of Virginia vs. Martin Shkreli*, No. 20CV00706 (DLC), 2022 WL 135026 (S.D.N.Y. Jan. 14, 2022).

⁶³⁹ There have been some new restrictions on drug pricing proposed, particularly at state level, to varying success. Interestingly, these have sometimes focused explicitly on off-patent drugs to avoid interfering with federal jurisdiction over patents. See e.g., Reed, Sydney, "Preventing Drug Price Gouging: Government Power and Initiatives" (2019) 19 *Houston Journal of Health Law & Policy* 165–194; Tessema, Frazer A, Aaron S Kesselheim & Michael S Sinha, "Generic but Expensive: Why Prices Can Remain High for Off-Patent Drugs" (2020) 71:4 *Hastings Law Journal* 1019–1052.

it can simply discontinue the product, or it may attempt to divest it to another party that might be interested in continuing production. Since there are no longer any patents, the divestment includes other repositories of value, such as tradenames and technical know-how, alongside the market approval itself. Not infrequently, the company initially receiving the divestment similarly finds the drug insufficiently lucrative (often despite a price hike) and divests it again. This happens until it lands in the lap of someone like Martin Shkreli.

While prominent innovator companies are themselves no strangers to high-priced new medicines, or to price increases on existing drugs, they have generally shied away from openly pushing the boundaries of extorting *de facto* monopolies on off-patent drugs to the same extremes. Nonetheless, they have played a crucial role in allowing it to occur. Even as Sir Andrew Witty, then-CEO of GSK, publicly criticized Turing's price increase for Daraprim, he failed to acknowledge that Daraprim was originally a GSK drug.⁶⁴⁰ Indeed, it remains a GSK product in much of the world. And it was GSK's divestment from Daraprim in North America, where it had constituted the only approved source of pyrimethamine, that ultimately allowed Turing to acquire the marketing rights in the first place (and, passing via CorePharma/Amedra Pharmaceuticals in between, resulted in its disappearance from the Canadian market). Nor was it the only such example under Witty's stewardship. As part of the same deal for the rights to pyrimethamine with CorePharma/Amedra Pharmaceuticals, GSK also transferred its rights to another Essential Medicine already encountered: albendazole (and the tradename Albenza).⁶⁴¹ Following albendazole's acquisition by CorePharma/Amedra, observers noted the "average wholesale price has increased by 3299%, from \$5.92

⁶⁴⁰ Ramsey, Lydia. "Big Pharma CEOs on Martin Shkreli: 'He is not us'", *Business Insider* (3 December 2015), online: <<http://www.businessinsider.com/big-pharma-ceos-distance-themselves-from-turings-martin-shkreli-2015-12>>.

⁶⁴¹ GlaxoSmithKline, "Important notification regarding Albenza® (albendazole) Tablets, Daraprim® (pyrimethamine) Scored Tablets and Dexedrine® (dextroamphetamine sulfate) Spansules (Class II)", online: <<https://www.gsk-ecs.com/gskstorefront/medias/2010-10-22-GlaxoSmithKline-Products-Divestment-Letter.pdf>>.

per typical daily dose in 2010 to \$201.27 in 2015” in the United States.⁶⁴² In the case of Albenza, there was no change in Canadian market status, as GSK had never bothered to seek market approval in the first place.⁶⁴³

Attracting less attention amidst the Shkreli media circus was the fact that the issue of divestment by originator companies had already been discussed by the US Senate Subcommittee on Aging shortly before pyrimethamine and cycloserine hit the headlines, in 2014 hearings with the title “Why are some generic drugs skyrocketing in price?”⁶⁴⁴ Unfortunately, while these hearings would presage the emergence of Martin Shkreli shortly thereafter, they would do little to prevent it. In testimony before the Subcommittee, Kesselheim described the situation, using albendazole as an example:

First, generic drug prices can rise because of a confluence of business decisions and profit-seeking from manufacturers. Take the case of albendazole, a broad-spectrum anti-parasitic medication first marketed by corporate predecessors to GlaxoSmithKline (GSK) outside the United States in 1982 and approved by the FDA in 1996.

Albendazole is rarely used in the United States, and the parasitic infections it treats usually only occur in poorer populations such as immigrants and refugees. Though its patents have expired, GSK remained the sole producer of the drug until the company sold its U.S. marketing rights to Amedra Pharmaceuticals, a small private firm, in October 2010. In 2011, Teva, the producer of the only potential

⁶⁴² Alpern, Jonathan D, John Song & William M Stauffer. “Essential Medicines in the United States — Why Access Is Diminishing” (2016) 374:20 N Engl J Med 1904–1907, online: <<http://www.nejm.org/doi/10.1056/NEJMp1601559>>.

⁶⁴³ Health Canada has publicly acknowledged that no application has ever been made to bring albendazole to market in a CBC news story in June 2021. See Kost, Hannah, “With clock ticking, doctors, pharmacists come to the rescue after 1-year-old eats raccoon feces”, *CBC News* (19 June 2021), online: <<https://www.cbc.ca/news/canada/calgary/raccoon-feces-roundworm-albendazole-1.6069633>>.

⁶⁴⁴ United States Senate, “Why are some generic drugs skyrocketing in price?” Hearing before the Subcommittee on Primary Health and Aging of the Committee on Health, Education, Labor and Pensions. (20 November 2014) S. Hrg. 113-859, online: <<https://www.govinfo.gov/content/pkg/CHRG-113shrg24459/html/CHRG-113shrg24459.htm>>.

therapeutically interchangeable competitor mebendazole (Vermox), discontinued production of its product for non-safety related reasons.⁶⁴⁵

In turn, Amedra acquired the rights to mebendazole from Teva in 2013.⁶⁴⁶ Some years before their investigation of drugs at risk of trolling, Alpern and colleagues had already remarked upon Amedra's price increase for albendazole and its acquisition of mebendazole, speculating that "Amedra's business strategy may be to corner a niche market for a pharmaceutical agent".⁶⁴⁷ When Impax purchased Tower Holdings (including CorePharma and Amedra) in 2015, the sale included both Albenza and Daraprim. Daraprim was sold on to Martin Shkreli and Turing, as previously discussed.⁶⁴⁸ Impax (now Amneal Pharmaceuticals Inc.) continues to sell albendazole in the United States at a price far above what it costs in much of the world.⁶⁴⁹ Only in 2020 was the first competing generic version approved in the US.

Thus, one potential juncture for intervention is in the original divestment. In an era where "Big Pharma" is often deployed as a pejorative, one might think originator companies would emphasize the Essential Medicines in their portfolios as a matter of self-interest. A demonstrated commitment to ensuring ongoing

⁶⁴⁵ United States Senate, "Why are some generic drugs skyrocketing in price?" Hearing before the Subcommittee on Primary Health and Aging of the Committee on Health, Education, Labor and Pensions. (20 November 2014) S. Hrg. 113-859, online:

<<https://www.govinfo.gov/content/pkg/CHRG-113shrg24459/html/CHRG-113shrg24459.htm>>.

⁶⁴⁶ It's worth noting the deal for mebendazole cost only \$3.5 million, albeit with an ongoing royalty. United States Securities and Exchange Commission, Form 10-K (Impax Laboratories, Inc.) (2016), online:

<https://www.annualreports.com/HostedData/AnnualReports/PDF/NASDAQ_IPXL_2016.pdf> at p.8.

⁶⁴⁷ Alpern, Jonathan D, William M Stauffer & Aaron S Kesselheim, "High-Cost Generic Drugs — Implications for Patients and Policymakers" (2014) 371:20 N Engl J Med 1859–1862, online: <<http://www.nejm.org/doi/10.1056/NEJMp1408376>>.

⁶⁴⁸ It's worth noting the deal for mebendazole cost only \$3.5 million, albeit with an ongoing royalty. United States Securities and Exchange Commission, Form 10-K (Impax Laboratories, Inc.) (2016), online:

<https://www.annualreports.com/HostedData/AnnualReports/PDF/NASDAQ_IPXL_2016.pdf> at p.55.

⁶⁴⁹ Shahriar, Arman A & Jonathan D Alpern, "Antiparasitic Drugs in the United States—Two Roads to High Prices" (2020) 5 Front Sociol 540478, online:

<<https://www.frontiersin.org/articles/10.3389/fsoc.2020.540478/full>>.

access to Essential Medicines, despite or even because of their low commercial appeal, would seem – at least to this author – like an easy public relations win, even before thinking of the benefits to human health. This strategy has worked for production and large-scale donation of Essential Medicines for Neglected Diseases for LMICs; indeed, GSK actively emphasizes its ongoing mass donations of albendazole to tackle Neglected Diseases like lymphatic filariasis.⁶⁵⁰ Such a strategy could work for vulnerable populations in high-income countries as well, especially as a counterweight to negative press around exorbitant domestic prices for newer, more lucrative drugs. There also seems little obvious downside to doing so, particularly in the case of a drug the same company continues to market elsewhere, beyond the costs associated with ensuring an existing drug remains available.⁶⁵¹ Nevertheless, corporate initiatives around Essential Medicines for Neglected Diseases have tended to focus exclusively on the most resource-poor settings. As just one example, in 2021, Sanofi announced the formation of a new venture, Sanofi Global Health:

Leveraging the company's diverse and large portfolio of medicines and global footprint, Sanofi Global Health is dedicated to increasing access to medicines considered essential by the World Health Organization (WHO) for patients in 40 lower income countries. Thirty of Sanofi's medicines will be provided across a wide range of therapeutic areas, including cardiovascular disease, diabetes, tuberculosis, malaria and cancer.⁶⁵²

⁶⁵⁰ GSK, *Neglected Tropical Diseases: Our commitment* (2021), online: <<https://www.gsk.com/media/6543/ntd-factsheet-jan2021.pdf>>.

⁶⁵¹ It is possible, at least hypothetically, that an Essential Medicines portfolio heavy on decades-old off-patent drugs might cast a shadow over more recent, less Essential products, raising uncomfortable questions about why a company stopped developing drugs for critical public health needs in favour of developing drugs for, say, male pattern baldness. It's not clear, however, that this strawman concern has ever materialized in reality.

⁶⁵² Sanofi, "Sanofi expands its social commitments, creates nonprofit unit to provide poorest countries with access to essential medicines" (7 April 2021), online: <<https://www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/media-room/press-releases/2021/2021-04-07-09-03-41-2205543-en.pdf>>.

To be clear, if this initiative comes to fruition, it seems a laudable effort; furthermore, low-resource, high-burden settings are both a logical and ethical first priority for improving access to medicines. Nonetheless, it also underscores industry disinterest in ensuring this same portfolio is simply made affordable and accessible to everyone who requires these drugs, wherever they are located; this is despite the fact that Sanofi will be producing the product regardless and has a large presence in high- and low-income countries alike. The identities of these 30 Essential Medicines were not included in the announcement and have still not materialized as of this writing; as such, it is impossible to determine the global market status of each, including whether they are currently marketed in high-income countries at all. Given what has been witnessed in this thesis thus far, however, there is a good chance that at least some of them are not available in countries like Canada.⁶⁵³

Commented [AH3]: Incl update?

While some companies emphasize donations or affordable access programs in LMICs for certain Essential Medicines, others have rested on their laurels while letting the actual drugs fall by the wayside. Take the Swiss pharma company Roche. On its website, under the heading “Developing essential medicines”, Roche states:

32 medicines developed by Roche are included in the WHO Model Lists of Essential Medicines. Thirty of these are patent-free and include many important antibiotics, anti-malarials and chemotherapy drugs.⁶⁵⁴

But when cross-referenced against Roche’s global product list, found elsewhere on the same website, it appears that Roche is currently in the business of selling only 11 of these Essential Medicines, or just over a third. None of the Essential Medicines it currently sells are for Neglected Diseases; only two are for infectious diseases of any kind. It is unclear how exactly Roche reached this point with its

⁶⁵³ For instance, Sanofi’s product portfolio includes malaria combination therapies that include artesunate, and the TB drug rifapentine.

⁶⁵⁴ This claim is based on the 2019 WHO EML. Roche, “Developing essential medicines”, online: *roche.com* <https://www.roche.com/sustainability/access-to-healthcare/ath_who.htm>.

Essential Medicines portfolio, but it is clear that its past achievements do not reflect its current practices.

As to why companies would abandon their portfolios of Essential Medicines, it has been suggested that there has been a philosophical shift in the practices of pharmaceutical companies in recent decades. In their report on Canadian drug shortages in 2011, CADTH suggested “It is believed that there was a time when global drug manufacturers protected certain service products in the interest of patient care... [i]t appears that this philosophy has changed”.⁶⁵⁵ Similar sentiments have been expressed elsewhere in the world:

For a long time it was much appreciated in the market that these multinational pharmaceutical companies had so-called service products: relatively small and commercially less interesting niche products that were made available as part of wide product range. It seems to us that there is a change in policy: when a product is deemed insufficiently profitable it is withdrawn without sufficient thought for the patients.⁶⁵⁶

Digging deeper, it appears that some of this idea of “public service drugs” may have ties to the greater regulatory burden placed upon pharmaceutical companies as a result of regulatory reforms undertaken in response to the thalidomide disaster of the early 1960s, as discussed elsewhere in this thesis.⁶⁵⁷ Indeed, such “‘orphan drugs’, with little commercial value to the suppliers, who often consider them as ‘service items’” that they have not brought to market in Canada are highlighted as constituting many of the drugs obtained via the SAP/EDRP in the mid-1980s.⁶⁵⁸ Nonetheless, while this added regulatory burden might help to explain issues both

⁶⁵⁵ Canadian Agency for Drugs and Technologies in Health (CADTH). *Drug Supply Disruptions*, Environmental Scan, by Canadian Agency for Drugs and Technologies in Health (CADTH), Environmental Scan Issue 17 (2011).

⁶⁵⁶ Yves Liem, TB et al., “Drug shortages in hospital pharmacy: experiences from Europe” (2004) 2 *European Journal of Hospital Pharmacy* 46–28.

⁶⁵⁷ See e.g., Shirkey, H, “Therapeutic orphans” (1968) 72:1 *J Pediatr* 119–120.

⁶⁵⁸ White, G.F. & M.J. Davis, “Antiparasitic drugs: availability and regulatory requirements for ‘emergency’ supply” (1985) 132:3 *Can Med Assoc J* 273–274.

with innovation for Neglected Diseases and subsequent market entry, it is less satisfactory when it comes to the discontinuation or divestment of drugs that have already received market approval. In such cases, the most burdensome work has already been done. Perhaps, then, it is a combination of shifts in both philosophy and regulatory burden. Yet as will be seen momentarily, even where the tension between profits and public health is actively considered in a divestment decision, the results are not always satisfactory.

Cycloserine & Capreomycin: Overlooked Consideration in Divestment

While examples of companies divesting themselves of Essential Medicines for Neglected Diseases have already been provided, the saga of two Essential Medicines for tuberculosis, one of them the drug which first sparked this thesis, helps chart the path of divestment in more detail at the global level. This story illustrates how high-income settings can be overlooked even where ensuring ongoing access in lower-income, higher-burden settings is an explicit consideration in the divestment of an Essential Medicine by the originator company.

Eli Lilly (Lilly) is a large American pharmaceutical company. As most businesses do, it makes decisions about whether to start selling some products and stop selling others. Some products may become unprofitable over time; others may still earn money, but less than the rollout of a new product using the same manufacturing facilities might. These are business decisions. However, when the products in question are medicines, especially Essential Medicines, such decisions have serious consequences that need to be a greater part of the decision-making process. What makes this particular example especially intriguing is that, unlike GSK's pyrimethamine and albendazole divestments, Lilly did explicitly take ongoing global access into account, at least as one factor under consideration. Furthermore, in doing so, Lilly's actions may legitimately have benefitted access in lower-income, higher-burden countries. In the United States and Canada, however, the result was not only a failure but an entirely predictable one, highlighting how high-income countries are overlooked in conversations about sustainable global access to old but Essential Medicines.

Cycloserine (tradename Seromycin) received FDA approval in the 1960s; Lilly brought another tuberculosis medicine, capreomycin (tradename Capastat), to market in 1971. Then, sometime in the late 1990s, Lilly decided it no longer wanted to produce these drugs it had developed. Why did Lilly want to stop making two medicines of such importance for treating drug-resistant TB? As the company itself puts it in a White Paper on the fates of the two drugs:

Over the course of its history, Lilly's product portfolio has evolved numerous times, and in the late 1990s, as the MDR-TB crisis grew, Lilly's portfolio was in the midst of another evolution. The manufacturing unit was preparing for a new wave of products, and management decisions included exiting a large number of older products that the company produced. Capreomycin and cycloserine were two of the products on that list; the market for these drugs was very small, and since the medicines were off patent, some manufacturers were already producing generic versions of them. Lilly planned to cease production in the near future.⁶⁵⁹

Underplayed in Lilly's White Paper is the fact that this is indeed where the story ends in some jurisdictions in the late 1990s; despite being the sole source of both cycloserine and capreomycin in Canada, the Health Canada Drug Database notes that Lilly discontinued both products in Canada in 1997. The White Paper instead focuses on the subsequent divestment of the drugs in other territories a few years later. In divesting themselves totally of these drugs, however, Lilly did something noteworthy. As described in the White Paper, in 2003, Lilly "decided to donate the intellectual property rights and manufacturing know-how for two Lilly antibiotics, capreomycin and cycloserine, that had been identified as effective in the treatment

⁶⁵⁹ Eli Lilly and Company, *Seeking Solutions to a Global Health Crisis Eli Lilly and Company's Technology Transfer for Multidrug-Resistant Tuberculosis Medicines*, White Paper, (Eli Lilly and Company, 2014) at p.3.

of MDR-TB”.⁶⁶⁰ A positive assessment of this statement is that Lilly recognized that the primary value of these drugs was not financial but medical, and that continued production was important for public health. A less charitable assessment is that Lilly tried to put a polite spin on offloading two insufficiently lucrative drugs. The truth may lie somewhere in the middle.

Between these two poles, there is tension visible in how the White Paper attempts to reconcile Lilly’s philanthropic framing with its image of the market. On the one hand, the Lilly MDR-TB Partnership would be “the largest philanthropic undertaking in the company’s history”.⁶⁶¹ On the other hand, rather than a valuable legacy product, the drugs are treated like a cross that Lilly has had to bear: “By 1996, capreomycin and cycloserine were used to treat fewer than 1,000 TB patients per year, and the company manufactured the drugs only intermittently. Some years, Lilly had no orders for capreomycin and cycloserine and made none at all”.⁶⁶² Furthermore, although “these drugs were already off-patent and Lilly was not the only supplier, Lilly was the only one approved by a stringent regulatory authority, and we continued to supply these drugs at prices well below our manufacturing costs”.⁶⁶³ Yet speaking of the same time period, within the same document, Lilly states that in “the late 1990s, the global production volume of quality-assured capreomycin and cycloserine was insufficient to meet the growing need for treatment of MDR-TB”.⁶⁶⁴ In other words, not enough high-quality drugs were produced to serve the increasing number of people who required them.

⁶⁶⁰ Eli Lilly and Company, *Seeking Solutions to a Global Health Crisis Eli Lilly and Company’s Technology Transfer for Multidrug-Resistant Tuberculosis Medicines*, White Paper, (Eli Lilly and Company, 2014) at p.1.

⁶⁶¹ Eli Lilly and Company, *Seeking Solutions to a Global Health Crisis Eli Lilly and Company’s Technology Transfer for Multidrug-Resistant Tuberculosis Medicines*, White Paper, (Eli Lilly and Company, 2014) at p.1.

⁶⁶² Eli Lilly and Company, *Seeking Solutions to a Global Health Crisis Eli Lilly and Company’s Technology Transfer for Multidrug-Resistant Tuberculosis Medicines*, White Paper, (Eli Lilly and Company, 2014) at p.6.

⁶⁶³ Eli Lilly and Company, *Seeking Solutions to a Global Health Crisis Eli Lilly and Company’s Technology Transfer for Multidrug-Resistant Tuberculosis Medicines*, White Paper, (Eli Lilly and Company, 2014) at p.7.

⁶⁶⁴ Eli Lilly and Company, *Seeking Solutions to a Global Health Crisis Eli Lilly and Company’s Technology Transfer for Multidrug-Resistant Tuberculosis Medicines*, White Paper, (Eli Lilly and Company, 2014) at p.3.

Unfortunately, given most of them were not in high-income countries, it appears this growing number of patients was not seen as a sufficiently enticing opportunity.

Given the importance pricing would come to play in this affair, it should also be noted at this juncture that a 2001 study in *Science* indicated that cycloserine prices (per tablet) ranged from an “international reference price (Boston, USA)” of \$8.42, to a high-income country average of \$3.38, to a low-income average of \$1.50, and a price via the Global Drug Facility (a mechanism discussed later) of \$0.14.⁶⁶⁵ It is true this latter price was subsidized by Lilly; indeed, global prices actually rose following Lilly’s divestment.⁶⁶⁶ Thus, there is certainly room to talk about sustainable pricing to ensure such drugs remain both available and affordable at the global level; however, even the “Boston” and HIC average prices of 2001 are a far cry from the eventual Rodelis price of \$360 per tablet.

Even more intriguingly, both cycloserine and capreomycin were first added to the WHO MEML (12th ed.) in 2002, the year before Lilly supposedly made its ultimate decision to divest by donation.⁶⁶⁷ The White Paper not only fails to acknowledge this development, it also never refers to Essential Medicines at all. Given the ostensibly philanthropic and public health themes of the White Paper, this is a puzzling omission. The end result, however, is that Lilly made the decision to divest at the same time it acknowledged that global demand for the drugs was increasing, and on the heels of the importance of these two drugs being underscored at the international level by their inclusion on the WHO MEML. Moreover, the inclusion of these and other medicines for DR-TB on the WHO MEML at the time did not occur in a vacuum. In a further illustration of the broader practical impacts of the WHO MEML, their inclusion came against a backdrop of explicit recognition of, and advocacy to draw attention to, the importance of

⁶⁶⁵ Gupta, R et al. “Responding to market failures in tuberculosis control” (2001) 293:5532 *Science* 1049–1051.

⁶⁶⁶ International Union Against Tuberculosis and Lung Disease & Médecins Sans Frontières, *DR-TB drugs under the microscope* (2011), online: <https://msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_report_UndertheMicro_ENG_2011.pdf>.

⁶⁶⁷ WHO Expert Committee on the Selection and Use of Essential Medicines, ed, *The selection and use of essential medicines: report of the WHO expert committee, 2002* WHO Technical Report Series 914 (Geneva: World Health Organization, 2003).

ensuring that sources of DR-TB drugs were of high quality.⁶⁶⁸ Accompanying this recognition of the importance of drug quality came a global procurement shift away from the cheapest available options towards using high-quality sources approved by a Stringent Regulatory Authority (SRA).⁶⁶⁹ As such, not only was demand for DR-TB treatment growing, but so was demand for a quality-assured supply; as Lilly itself noted, it was the only manufacturer of cycloserine and capreomycin meeting this standard at the time.⁶⁷⁰

Lilly's divestment considerations are also framed somewhat differently in a 2015 interview with one of the Lilly executives responsible in the World Intellectual Property Organization's *WIPO Magazine*.⁶⁷¹ Published in May of that year, it ironically predates the Rodelis pricing fiasco by just a few months. In the interview, the emphasis is placed not on a small market for which Lilly might not even manufacture the drugs every year, as in the White Paper, but on Lilly not having the capacity to produce the high volumes required to treat the estimated 450,000 new cases of MDR-TB each year.⁶⁷² At the same time, the interviewee once again underscores the gulf between commercial and health concerns, stating "notwithstanding a huge medical need, there was simply no market for these drugs".⁶⁷³ It is also notable that the interview entirely omits any reference to the spectacular failure of the divestment initiative's American arm, discussed below, which had been readily apparent for years before the interview, and was setting the stage for Rodelis to enter the scene.

⁶⁶⁸ See e.g., Gupta, R et al., *Proceedings from the Procurement of Second-Line Anti-Tuberculosis Drugs for DOTS-Plus Pilot Projects*, Cambridge, MA, 5 to 6 July 1999, R. Gupta et al., Eds. (WHO, Geneva, 2000).

⁶⁶⁹ This issue, and the role of WHO Prequalification in assuring quality, will be returned to later in this thesis.

⁶⁷⁰ Eli Lilly and Company, *Seeking Solutions to a Global Health Crisis Eli Lilly and Company's Technology Transfer for Multidrug-Resistant Tuberculosis Medicines*, White Paper, (Eli Lilly and Company, 2014) at p.7.

⁶⁷¹ Jewell, Catherine, "Tackling multi-drug resistant tuberculosis: lessons in technology transfer" *WIPO Magazine* (May 2015), online: https://www.wipo.int/wipo_magazine/en/2015/02/article_0007.html.

⁶⁷² Jewell, Catherine, "Tackling multi-drug resistant tuberculosis: lessons in technology transfer" *WIPO Magazine* (May 2015), online: https://www.wipo.int/wipo_magazine/en/2015/02/article_0007.html.

⁶⁷³ Jewell, Catherine, "Tackling multi-drug resistant tuberculosis: lessons in technology transfer" *WIPO Magazine* (May 2015), online: https://www.wipo.int/wipo_magazine/en/2015/02/article_0007.html.

Whatever its actual reasons for divesting, once it made its decision to do so, Lilly then reached out to potential divestees. Given the global burden of TB, it makes sense that the focus of the White Paper is on manufacturers in middle-income countries with both pharmaceutical production capacity and high burdens of TB, with companies identified in Russia, India, China and South Africa. However, the comparative lack of attention did not bode well for the high-income, low-burden United States, where the rights to capreomycin and cycloserine were split up, with capreomycin going to Akorn Pharmaceuticals and cycloserine going to the Chao Center at Purdue University.

Akorn Pharmaceuticals largely stayed out of the headlines. It continued to provide capreomycin to the Global Drug Facility, albeit at a higher cost than Lilly had.⁶⁷⁴ Here it should be observed that capreomycin is a prime example of a medicine that is an Essential Medicine only until something superior comes along. It is not a pleasant drug; its serious side effects can include kidney damage and hearing loss.⁶⁷⁵ However, in the decades during which no new tuberculosis drugs were developed and the number of DR-TB cases increased, it became Essential. Ultimately, novel drugs like bedaquiline and delamanid emerged in the 2010s; as of 2019, capreomycin was no longer recommended for treatment of MDR-TB under the updated WHO guidelines for treating DR-TB.⁶⁷⁶ Similarly, it was removed from the WHO's Model List of Essential Medicines in 2019 as part of a broader shift away from injectable treatments for drug-resistant tuberculosis. According to the FDA Drug Shortages database, Akorn discontinued capreomycin in May of 2021; it is now absent from the American market. In this instance, its discontinuation as a

⁶⁷⁴ Brigden, Tania, "Capreomycin shortage: symptom of a bigger problem in multidrug-resistant tuberculosis", (19 July 2011), online: *PLOS Blogs - Speaking of Medicine and Health* <<https://speakingofmedicine.plos.org/2011/07/19/capreomycin-shortage-symptom-of-a-bigger-problem-in-multidrug-resistant-tuberculosis/>>; Moon, Suerie et al., "A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries" (2011) 7:1 Global Health 39, online: <<http://globalizationandhealth.biomedcentral.com/articles/10.1186/1744-8603-7-39>>.

⁶⁷⁵ See e.g., Arnold, Amber et al., "Adverse Effects and Choice between the Injectable Agents Amikacin and Capreomycin in Multidrug-Resistant Tuberculosis" (2017) *Antimicrob Agents Chemother* 61:9.

⁶⁷⁶ World Health Organization. *WHO consolidated guidelines on drug-resistant tuberculosis treatment*. (2019).

drug superseded by newer, better drugs and no longer recommended in international standards is entirely appropriate – with the major caveat that those alternatives need to be available in its stead.⁶⁷⁷ Fittingly, it also disappears from the tale now being related.

The bigger story is what happened to cycloserine at the Chao Center. It appears Purdue University had long figured into Lilly's divestment plans. In 2003, around the time of Lilly's initial divestment decision and a decade before the White Paper, an announcement of the "Purdue-Lilly Partnership" already outlined the increased need for cycloserine for TB treatment, but quite blatantly states "the required increase in production would not generate sufficient revenue for Lilly to make it worthwhile".⁶⁷⁸ At the same time, it also counterintuitively sets out the expectation that making this drug would be a profitable enterprise for Purdue: "Since they will be relatively small, the amounts of Seromycin produced by the Purdue facility will not outstrip its capacity, but, at the same time, they will yield a profit necessary to fund the facility".⁶⁷⁹ A Purdue University news story at the time similarly suggests that the university thought it would be able to "generate significant revenue".⁶⁸⁰ Given that the Chao Center had never previously manufactured any drug, that its portion of the global market was the low burden USA, and that Lilly was eager to wash its hands of a drug it viewed as no longer worthwhile, Purdue's hopes in this regard seem somewhat ambitious. Still, the other, non-financial, opportunities presented by the arrangement, such as

⁶⁷⁷ Of the two new drugs mentioned, bedaquiline and delamanid, only the former is formally marketed in the United States; a third novel drug, pretomanid, was approved by the FDA in 2019. None of these drugs are formally available in Canada.

⁶⁷⁸ Purdue University. *The Purdue-Lilly Partnership* (2 October, 2003), online (cached): <<https://web.archive.org/web/20070703143755/https://www.ippu.purdue.edu/News/preview.cfm?ArticleID=115>>.

⁶⁷⁹ Purdue University. *The Purdue-Lilly Partnership* (2 October, 2003), online (cached): <<https://web.archive.org/web/20070703143755/https://www.ippu.purdue.edu/News/preview.cfm?ArticleID=115>>.

⁶⁸⁰ Purdue University. *Purdue center takes on North American battle against multidrug-resistant tuberculosis* (11 December 2007), online: <<https://www.purdue.edu/uns/x/2007b/071211HornettChao.html>>.

providing practical experience to Purdue students, may also have been important considerations.⁶⁸¹

The transfer did not officially occur until a few years later, in 2007. By 2010, just three years after the transfer occurred (and four years before the White Paper), it was announced that the Chao Center would close, having failed to become a self-sustaining enterprise.⁶⁸² It was generating about \$1 million a year in revenue, against \$2 million in annual expenses.⁶⁸³ This is unsurprising given not only that cycloserine remained the only drug produced at Chao, but that production runs occurred only once a year, taking one to two weeks.⁶⁸⁴ As a consequence:

The Center's manufacturing capabilities are dormant for most of the year. Despite this, the Center incurs substantial costs throughout the year. It must pay the salary of three fulltime employees, pay full GDUFA [Generic Drug User Fee Act] fees of approximately \$250,000 a year, rent space, and service the infrastructure required to comply with FDA manufacturing regulations.⁶⁸⁵

On the one hand, this does highlight a legitimate issue in how fees designed with major producers of lucrative drugs in mind can impose a burden on small producers of more marginal products. On the other, it underscores questions about Chao's business plan, and Lilly's genuine commitment to ensuring continued

⁶⁸¹ Purdue University. *The Purdue-Lilly Partnership* (2 October, 2003), online (cached): <<https://web.archive.org/web/20070703143755/https://www.ippu.purdue.edu/News/preview.cfm?ArticleID=115>>.

⁶⁸² Macdonald, Gareth. "Chao Center to close; replacement Seromycin maker required", (27 April 2010), online: <<https://www.outsourcing-pharma.com/Article/2010/04/28/Chao-Center-to-close-replacement-Seromycin-maker-required>>.

⁶⁸³ United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System* (United States Senate, 2016).

⁶⁸⁴ United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System* (United States Senate, 2016).

⁶⁸⁵ GUDFA is the *Generic Drug User Fee Act*, which since 2012 has required generic drug makers to pay annual fees to support FDA services. United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System* (United States Senate, 2016).

production via divestment. Despite its financial circumstances, Chao agreed to continue to produce cycloserine until a new producer was identified.⁶⁸⁶ It was not until 2015 that such a producer could be found; that it took this long to find a willing taker for a *de facto* monopoly over an Essential Medicine in the world's most lucrative pharmaceutical market further demonstrates the weaknesses of reliance on the market to fill such gaps. On August 19 of that year, the Chao Center finally transferred marketing authorization and other rights, like the tradename Seromycin, to the Dublin-based Rodelis, who, as related in the opening pages, promptly hiked its price twenty-fold. Unsurprisingly, a sizeable price hike was a very foreseeable part of the transfer for both Chao and Rodelis; testimony before the US Senate Commission indicates that communications "between the parties prior to closing indicate that both parties viewed the ability to substantially raise prices on Seromycin as a key transaction selling point".⁶⁸⁷ Nonetheless, the speed and size of the increase may have come as a surprise to all but Rodelis; the 5000% price hike occurred within a matter of days.

In this instance, protests and ensuing bad publicity caused something unusual: a partial reversal.⁶⁸⁸ On September 21, 2015, the Chao Center announced that it had re-acquired the rights from Rodelis.⁶⁸⁹ Per the official announcement: "Following a substantial increase in the cost of Cycloserine by Rodelis, it became clear that the Rodelis strategy was not consistent with the Chao Center's expectations or vision".⁶⁹⁰ The announcement also contains a reasonable

⁶⁸⁶ "North America's Sole Manufacturer of MDR-TB Drugs Closing Its Doors", *Working Group on New TB Drugs* (26 April 2010), online: <<https://www.newtbdrugs.org/news/north-america%E2%80%99s-sole-manufacturer-mdr-tb-drugs-closing-its-doors>>.

⁶⁸⁷ United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System* (United States Senate, 2016).

⁶⁸⁸ Pollack, Andrew. "Big Price Increase for TB Drug Is Rescinded", *New York Times* (22 September 2015), online: <<http://www.nytimes.com/2015/09/22/business/big-price-increase-for-tb-drug-is-rescinded.html>>.

⁶⁸⁹ *Chao Center Reacquires Rights to Cycloserine* (September 21, 2015), online: <https://www.tbonline.info/media/uploads/documents/chao_center_reacquires_rights_to_cycloserine.pdf>.

⁶⁹⁰ *Chao Center Reacquires Rights to Cycloserine* (September 21, 2015), online: <https://www.tbonline.info/media/uploads/documents/chao_center_reacquires_rights_to_cycloserine.pdf>.

observation, echoing previous difficulties, regarding the fate of off-patent Essential Medicines in small markets:

Chao Center officials encourage an ongoing discussion with FDA, CDC, WHO and other health and safety organizations to more deeply pursue the need for support and allowances for small, legacy and orphan drug manufacturers with new ways to maintain drugs like Cycloserine. If manufacturers are to keep these drugs in production for the low-volume, high-need patient, then the drugs should be handled much differently than the blockbuster drugs of high volume to assure patient access.⁶⁹¹

The bittersweet conclusion to the announcement, however, is that while it immediately dials back the Rodelis price, it offers a new one of its own: “Effective immediately the price per blister pack of Cycloserine is \$1,050 (\$35 a capsule*30 capsules)”, or just over twice the price of that same blister pack prior to the initial Rodelis transfer.⁶⁹²

Thus ends the saga of Eli Lilly’s tuberculosis drug divestment in North America (well, almost; the Chao Center has since rebranded twice, first as PGC in 2017, and then as Parsolex in 2019, although it is still affiliated with Purdue University and remains the sole FDA-approved producer of cycloserine as of this writing).⁶⁹³ Broadly speaking, whatever its underlying motive(s), the ostensible premise of Lilly’s TB initiative was not without merit, particularly when contrasted

⁶⁹¹ *Chao Center Reacquires Rights to Cycloserine* (September 21, 2015), online: <https://www.tbonline.info/media/uploads/documents/chao_center_reacquires_rights_to_cycloserine.pdf>.

⁶⁹² *Chao Center Reacquires Rights to Cycloserine* (September 21, 2015), online: <https://www.tbonline.info/media/uploads/documents/chao_center_reacquires_rights_to_cycloserine.pdf>.

⁶⁹³ Veleta, Kylie, “Chao Center Becomes PGC, Now Open for Business”, *Inside Indiana Business* (29 June 2017), online: <<https://www.insideindianabusiness.com/story/35778210/chao-center-becomes-pgc-now-open-for-business>>; Purdue University. “Purdue GMP Center now operates as Parsolex and is expanding capabilities”, (29 October 2019), online: <<https://www.purdue.edu/newsroom/releases/2019/Q4/purdue-gmp-center-now-operates-as-parsolex-and-is-expanding-capabilities.html>>.

with the purely commercial divestments of other originator companies like GSK. Sharing expertise to increase global manufacturing capacity and volume, with the end goal of “[e]stablishing a sustainable, long-term, high-quality supply of capreomycin and cycloserine” are all laudable objectives.⁶⁹⁴ Similarly, even if the Chao Center seems a questionable choice of partner to meet those objectives effectively, the Chao Center’s own approach – producing a drug of recognized importance serving a small market as part of an educational university program – is also a potentially appealing one in theory if not, at least in this particular instance, in execution.

It must also not be overlooked that at the global level it appears there have been some positive outcomes to Lilly’s divestment program, which may well outweigh the North American fiasco, both karmically and in terms of a net gain for global health. As noted, the global price for both drugs initially went up following the divestment.⁶⁹⁵ However, within a few years, there were multiple WHO Prequalified sources of drugs for which Lilly had once been the only quality-assured manufacturer. For instance, following the transfer from Lilly, cycloserine from the Russian company Biocom became the first product from a Russian manufacturer to receive WHO Prequalification, providing assurances of quality while allowing it to reach a wider global market (and more importantly from a health perspective, more patients).⁶⁹⁶ However, the fact remains that Lilly neglected to take measures it could have taken to ensure a sustainable solution in the American market as well (even without considering the earlier discontinuation of the drug in Canada). It must also not be forgotten that in the end it was the Chao

⁶⁹⁴ Eli Lilly and Company, *Seeking Solutions to a Global Health Crisis Eli Lilly and Company’s Technology Transfer for Multidrug-Resistant Tuberculosis Medicines*, White Paper, (Eli Lilly and Company, 2014) at p.4.

⁶⁹⁵ Moon, Suerie et al., “A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries” (2011) 7:1 Global Health 39, online: <<http://globalizationandhealth.biomedcentral.com/articles/10.1186/1744-8603-7-39>>; International Union Against Tuberculosis and Lung Disease & Médecins sans frontières, *DR-TB drugs under the microscope* (2011), online: <https://msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_report_UndertheMicro_ENG_2011.pdf>.

⁶⁹⁶ Eli Lilly and Company, *Seeking Solutions to a Global Health Crisis Eli Lilly and Company’s Technology Transfer for Multidrug-Resistant Tuberculosis Medicines*, White Paper, (Eli Lilly and Company, 2014) at p.14.

Center who, despite their limited resources (and failing business model), reclaimed cycloserine from its exploitative new owners at Rodelis. Lilly, with its considerably greater resources, does not appear to have lifted a finger to support its legacy Essential Medicine or the goals professed in its divestment when the drug was being very publicly exploited; indeed, it seems to have disclaimed any influence over the situation.⁶⁹⁷

This story thus raises bigger questions about what a company should do with its less profitable legacy drugs. Should it celebrate them? Does it owe humanity something as part of that legacy? Do pharmaceutical companies have their own human rights obligations under international law?⁶⁹⁸ According to Lilly's White Paper, the "largest philanthropic undertaking in the company's history" cost "\$170 million in cash, medicine, and training" between 2003 and 2016.⁶⁹⁹ In other words, it cost an average of \$12 million per year over a 14-year period; for 2016 alone, Eli Lilly reported worldwide revenue of \$21.222 billion, and a net income of \$2.738 billion.⁷⁰⁰ It could easily have afforded to continue producing the drug itself had it wished to do so; it could even have expanded production to meet the recognized global need. This would not have been the most lucrative decision, but nor would it have had any real impact on the bottom line of a corporation reaping billions in profits; its large philanthropic undertaking could instead have been to continue, and indeed expand, its own production.

And if Lilly still chose to divest, it should have done so differently. First, partitioning its global assets could have been done in a manner that did not isolate a small, potentially unsustainable American market. Incorporating the American market into a larger territory could help sustain the market while perhaps also

⁶⁹⁷ "Tuberculosis drug price jumps 2,000%, shocks doctors", *CBC News* (21 September 2015), online: <<https://www.cbc.ca/news/health/tb-drug-price-cycloserine-1.3237868>>.

⁶⁹⁸ This thesis will not delve into the issue of corporate human rights obligations. There is, however, a dearth of legally enforceable obligations for pharmaceutical companies under international law. For a helpful if slightly dated introduction to this topic, see Lee, Joo-Young & Paul Hunt, "Human rights responsibilities of pharmaceutical companies in relation to access to medicines" (2012) 40:2 *J Law Med Ethics* 220–233.

⁶⁹⁹ Eli Lilly and Company, *Seeking Solutions to a Global Health Crisis Eli Lilly and Company's Technology Transfer for Multidrug-Resistant Tuberculosis Medicines*, White Paper, (Eli Lilly and Company, 2014) at p.1.

⁷⁰⁰ *Lilly Reports Fourth-Quarter and Full-Year 2016 Results* (Eli Lilly and Company, 2017).

offering a toehold into the American market for the new manufacturer as a further incentive. This in turn could have been used to help integrate product standards to ensure drugs produced primarily for other regions met American SRA standards. Given the importance that had already been placed on the global need not merely for TB drugs but for high-quality TB drugs, this seems an obvious consideration. Secondly, Lilly could have structured its divestments so as to retain some control over Essential Medicines that should be jewels, even if dusty ones, in its portfolio. As noted in media coverage of the Rodelis debacle, both Lilly and Chao protested they retained no legal control over the pricing of the divested drug.⁷⁰¹ However, one relatively simple means of maintaining such control would have been through licensing, rather than transferring, intellectual property such as tradenames.⁷⁰² A tradename, particularly for a sole-source product like Seromycin known to many physicians and patients by that name, retains value.⁷⁰³ It could even go further and simply subcontract the entire package of IP and market authorization. A generous arrangement with only a few strings to prohibit egregious or exploitive conduct, or to regain control where a divestment winds up a failure rather than permit the onward transfer of the rights further downstream to less scrupulous parties, would provide leverage to prevent such conduct without unduly interfering with the new manufacturer. Admittedly, adding strings, even loose ones, to low-margin drugs may make such deals less appealing to the other party, but such strings could be limited to extreme scenarios. Certainly, in a case like Lilly, where the divestment

⁷⁰¹ Paul, Joseph, "Purdue Research Foundation familiar with drug price hike controversy", *Indianapolis Star* (22 September 2015), online: <<https://www.indystar.com/story/money/2015/09/22/purdue-research-foundation-familiar-drug-price-hike-controversy/72637110/>>; "Tuberculosis drug price jumps 2,000%, shocks doctors", *CBC News* (21 September 2015), online: <<https://www.cbc.ca/news/health/tb-drug-price-cycloserine-1.3237868>>.

⁷⁰² Intriguingly, the US Patent and Trademark Office shows that the trademark Seromycin (serial number 72016353), first registered by Eli Lilly in 1957, was cancelled by its last listed owner, Purdue GMP Center, in March 2020; a new trademark for Seromycin (serial number 88630156), encompassing a broader range of uses beyond tuberculosis including psychiatric and neurological disease, was filed by its successor, Parsalex GMP Center, in September 2019. Though beyond the scope of this thesis, here is an instance where novel uses may impact existing ones in the future.

⁷⁰³ For an intriguing take on the tradename issue, see Sarpatwari, Ameet & Aaron S Kesselheim, "The Case for Reforming Drug Naming: Should Brand Name Trademark Protections Expire upon Generic Entry?" (2016) 13:2 *PLoS Med* e1001955, online: <<https://dx.plos.org/10.1371/journal.pmed.1001955>>.

was made at no charge to the recipient, incorporating such terms seems entirely reasonable.

The cycloserine story is a prime example of how market failures belie medical importance. Where the market is not commercially appealing, solutions that are stubbornly market-based are going to be imperfect at best, and useless at worst. Meanwhile, existing market mechanisms can be exploited by the likes of Martin Shkreli. Alpern and colleagues conclude (and it seems hard to disagree):

[F]or-profit pharmaceutical companies remain unreliable sources for drugs that are essential to human health but have limited profit-generating potential. For drugs with these characteristics, the market is broken because companies either corner the market and charge “what the market will bear,” or sell the drug at a reasonable price, which limits profitability. In the latter example, withdrawal from the market becomes a risk [...]. Therefore, relying on the free market for a rational solution seems futile and other policy solutions are needed.”⁷⁰⁴

Before turning to such solutions, however, it should also be accepted – including by access to medicines advocates – that raising the price of a drug by a certain amount may at times be necessary to ensure its sustainability. Low prices themselves have been linked to shortages of generic drugs.⁷⁰⁵ The commercial motivations of companies have been outlined already, but there is a difference between a marginally profitable drug and a genuinely money-losing one. This is important to recognize, particularly when price increases are prone to be framed as having an inevitably negative impact on access; while a grotesque price hike can have as great an effect on access in practical

⁷⁰⁴ Alpern, Jonathan D, Stephen J Dunlop & William M Stauffer. “Broken drug markets in infectious diseases: Opportunities outside the private sector?” (2019) 13:4 PLoS Negl Trop Dis e0007190, online: <<https://dx.plos.org/10.1371/journal.pntd.0007190>>.

⁷⁰⁵ Dave, Chintan V et al., “Predictors of Drug Shortages and Association with Generic Drug Prices: A Retrospective Cohort Study” (2018) 21:11 Value Health 1286–1290.

terms as disappearance from the market, a smaller price hike to ensure sustainability will generally be preferable to discontinuance. It is also perfectly reasonable to expect a higher price in a HIC for a drug that retails for pennies in LMICs.⁷⁰⁶ That said, price increases frequently don't stop at sustainability; off-patent trolling is merely an extreme end of that trend. And in a *de facto* monopoly over a small market, there is no competition to keep prices low, let alone the race to the bottom pricing of competing tenders for major procurement contracts; this means key levers that normally apply to drug pricing aren't readily available.

Innovator pharmaceutical companies have received plenty of criticism for their conduct in recent decades, particularly on issues like global access to affordable antiretrovirals for HIV treatment, but even they sought to publicly distance themselves from the likes of Martin Shkreli.⁷⁰⁷ Nonetheless, as described above, originator companies do bear some responsibility for off-patent trolling, just as they do for their decisions to discontinue Essential Medicines, or not to introduce them into certain markets in the first place. When it comes to off-patent trolling, originator companies could and should do more to prevent irresponsible divestments ending up in the hands of unscrupulous hucksters, including refraining from divestment in the first place. They could also do more to actively ensure production and combat the seemingly less headline-friendly but ultimately even worse consequence of the drugs simply disappearing from the market entirely,

⁷⁰⁶ Issues like tiered global pricing for pharmaceuticals have been controversial, and an in-depth exploration is beyond the scope of this thesis. However, tiered pricing is another access issue inverted by the issue of access to off-patent Essential Medicines for Neglected Diseases in low-burden HICs. Traditionally, tiered pricing is anchored to a high price in HICs that are the primary commercial market; concessions are then given on the price for lower-income markets. There are a range of issues with this; see e.g., Moon, Suerie et al., "A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries" (2011) 7:1 Global Health 39, online: <<http://globalizationandhealth.biomedcentral.com/articles/10.1186/1744-8603-7-39>>. However, in the current instance, the anchor price for the primary market is generally LMICs; as such, it could be possible to structure tiering accordingly, premised on equitable pricing, with a focus on affordable yet sustainable access in contexts with different health resources. Indeed, higher prices in HICs can potentially help support sustainability in LMICs.

⁷⁰⁷ "An unusual business" (2015) 33:11 Nat Biotechnol 1113–1113, online: <<http://www.nature.com/articles/nbt.3409>>.

even as patients still need them. When they don't, however, further measures by the state may be necessary.

Chapter 7: An international problem with domestic aspects

Drug Shortages

At its core, this thesis focuses upon access to off-patent Essential Medicines for Neglected Diseases in Canada. In doing so, however, it illustrates how these drugs exemplify broader issues within the pharmaceutical regulatory system, and how similar problems are encountered in other HICs. In turn, such concerns arise against the backdrop of the wider national and international issue of drug shortages, a problem that is itself exemplified by off-patent Essential Medicines. To be clear, not all medicines facing shortages are off-patent or Essential Medicines, nor are these shortages restricted to drugs with small markets or a single supplier. However, off-patent Essential Medicines with limited or no competition are particularly vulnerable to such shortages.⁷⁰⁸ This extends far beyond Canada, and indeed beyond HICs; as noted in a report by the WHO Secretariat to the World Health Assembly in 2016, “Shortages of essential medicines are being documented in most parts of the world with increasing frequency. Many shortages have been linked to products that are older, off-patent or difficult to formulate [...] and few manufacturers (or a sole manufacturer)”.⁷⁰⁹ While tackling the problem of drug shortages in its entirety is well beyond the scope of this thesis, the fact remains that access to off-patent Essential Medicines and the issues underpinning drug shortages are linked. Both are also areas where as basic a step as simply establishing a list of important drugs is useful in resolving, or at least more effectively mitigating, the problem.

In broaching the topic of shortages, this section will also look at how the issue of global shortages has helped to reshape the role of the Canadian federal government over the past decade in dealing with medicines not effectively supplied by the market. Over this period, the federal government has shifted from insisting

⁷⁰⁸ Greene, Jeremy A, Gerard Anderson & Joshua M Sharfstein. “Role of the FDA in Affordability of Off-Patent Pharmaceuticals” (2016) 315:5 JAMA 461, online: <<http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2015.18720>>.

⁷⁰⁹ World Health Assembly, *Addressing the global shortages of medicines, and the safety and accessibility of children’s medication*, Sixty-Ninth World Health Assembly Report by the Secretariat A69/42 (World Health Organization, 2016) at para. 3.

that it has no role in tackling shortages, to enacting reforms that provide a better picture of shortages in Canada, to more aggressive (albeit narrowly targeted) measures to address shortages during the COVID-19 pandemic. These reforms have highlighted Essential Medicines and incorporated measures promoting easier access to unmarketed drugs. They have not yet, however, led to systemic changes in how unmarketed Essential Medicines are accessed, whether through formal approval or via other channels.

The specific shortages that initially catalyzed attention to the issue in Canada occurred in the early 2010s, and were most prominently associated with off-patent injectable medicines; these are more complex to make than other forms of drugs such as pills, and as a result attract fewer market entrants.⁷¹⁰ The Canadian Agency for Drugs and Technologies in Health (CADTH) highlighted the injectables shortage in early 2011.⁷¹¹ These shortages were not restricted by national borders; the United States, for instance, was also impacted by shortages of injectables at the time.⁷¹² In an FAQ on the shortages, Health Canada publicly stated that its authority “does not extend to forcing companies to bring a product to the Canadian market or maintaining sufficient supplies to meet the needs of patients”.⁷¹³ On March 14, 2012, the New Democratic Party (NDP) proposed a motion in the House of Commons, which passed unanimously. It stated:

That, in the opinion of this House, the government should: (a) in cooperation with provinces, territories and industry, *develop a nationwide strategy to anticipate, identify, and manage shortages of*

⁷¹⁰ Chabner, Bruce A. “Drug Shortages — A Critical Challenge for the Generic-Drug Market” (2011) 365:23 N Engl J Med 2147–2149, online: <<http://www.nejm.org/doi/abs/10.1056/NEJMp1112633>>.

⁷¹¹ Canadian Agency for Drugs and Technologies in Health (CADTH). *Drug Supply Disruptions*, Environmental Scan, by Canadian Agency for Drugs and Technologies in Health (CADTH), Environmental Scan Issue 17 (2011).

⁷¹² While this section will not delve into the American response to this shortage in detail, new measures in response to the shortages, particularly around reporting requirements, were introduced President’s Executive Order 13588 of Oct. 31, 2011, and codified the following year in the *Food and Drug Administration Safety and Innovation Act* of 2012.

⁷¹³ Health Canada, “Web info sheet on Drug Shortages” (11 November 2011), online (cached): <<https://www.webcitation.org/63zg4pf9K>>.

essential medications; (b) require drug manufacturers to report promptly to Health Canada, the provinces and the territories any planned disruption or discontinuation in production; and (c) expedite the review of regulatory submissions in order to make safe and effective medications available to the Canadian public [*emphasis added*].⁷¹⁴

Although Canada would fall short of meeting all the demands in this motion, some of these ideas would carry over into the subsequent work of the Parliamentary Standing Committee on Health (HESA), which undertook to study the issue. Some months later, HESA released a report identifying reasons behind the shortages:

Disruptions in supply can include the discontinuation of a pharmaceutical, as well as the interruption or reduction in production levels of a pharmaceutical. With respect to discontinuations, the Committee was told that generic medicines have a small profit margin, making it difficult to source raw materials and active pharmaceutical ingredients (APIs), or manufacturers may simply choose to terminate less profitable product lines. It also heard that mergers of drug manufacturing companies with similar product lines may result in consolidation and therefore change a multi-source product into a single-source product. Discontinuations of approved drugs are a foreseeable occurrence.⁷¹⁵

At this point, these reasons should come as little surprise to the reader. Furthermore, the commercial considerations behind market entry and exit are frequently made after considering factors outside of any one particular market; the

⁷¹⁴ House of Commons, Vote #163 on March 14th, 2012, online: <<https://openparliament.ca/votes/41-1/163/>>.

⁷¹⁵ Standing Committee on Health, Drug Supply in Canada: A Multi-Stakeholder Responsibility, 41st Parliament, 1st Session (2012), online: <<https://www.ourcommons.ca/Content/Committee/411/HESA/Reports/RP5640047/hesarp09/hesarp09-e.pdf>> at p.6.

increasingly complex international supply chains that undergird the global pharmaceutical industry are fueled by efforts to keep expenses as low as possible, such as through off-shoring production to less expensive locations.⁷¹⁶ Generic drugs lack the same protections from competition as those still under patent; this is one reason they are particularly likely to be “produced as inexpensively as possible, using older and less efficient production facilities, and with limited inventories to reduce carrying costs for the company”.⁷¹⁷ This puts such drugs in a more precarious position should disruptions occur; in turn, complex international supply chains create new opportunities for this to happen. Access to a drug in Canada could rely upon a Swiss company whose product is manufactured in India at a factory that is dependent on China for supplies of the Active Pharmaceutical Ingredient. Even widely used medicines with numerous producers, like the painkiller (and Essential Medicine) ibuprofen, are not immune from global trends.⁷¹⁸ Drugs with fewer manufacturers are even more easily affected. In turn, the introduction of some unanticipated element – a mechanical breakdown on a production line in one country, a border closure in another – can disrupt the whole system.

Some such disruptions may be out of any one party’s control. One recent high-profile illustration of such a disruption involving an off-patent Essential Medicine came in the form of Hurricane Maria in 2017, when US dependence on storm-damaged Puerto Rico for its supply of saline solution became all too apparent.⁷¹⁹ In that case, a single natural disaster had a dramatic impact on a

⁷¹⁶ Acosta, Angela et al. “Medicine Shortages: Gaps Between Countries and Global Perspectives” (2019) 10 *Front Pharmacol* 763.

⁷¹⁷ Chabner, Bruce A. “Drug Shortages — A Critical Challenge for the Generic-Drug Market” (2011) 365:23 *N Engl J Med* 2147–2149, online: <<http://www.nejm.org/doi/abs/10.1056/NEJMp1112633>>.

⁷¹⁸ Das, Sohini, “Ibuprofen API prices jump 30% in international market due to supply crunch”, *Business Standard* (22 August 2018), online: <https://www.business-standard.com/article/companies/ibuprofen-api-prices-jump-30-in-international-market-due-to-supply-crunch-118082101320_1.html>. There are at least eight companies currently marketing products containing ibuprofen in Canada, in more than 70 different forms.

⁷¹⁹ In this case, the Essential Medicine in question is literally salt water (though ensuring its sterility is a notably more complex manufacturing process than the simple ingredients list would suggest, in turn underpinning the lack of backup manufacturing capacity). Saline solution is a very widely used product indispensable for hospitals, whether for administering a medical infusion or being used for

product sold, if not at a high price, at least in high volume, and without particularly rare raw materials. Here too, while most attention focused on the US market, Canada was affected.⁷²⁰ Natural disasters are not the only disruptors, however; a business decision can also exert similar effects. As highlighted in the 2011 CADTH report, industry “mergers and consolidations resulting in single-source products, business decisions to discontinue manufacturing of minimally profitable products and just-in-time inventory management practices across the supply chain can amplify the effects of drug shortages”.⁷²¹ Where an inexpensive drug serves a small market, there is even less incentive to invest in making it. As such, a present or predicted decrease in demand as a consequence of decreased incidence of a disease can also be a driver for such decisions.⁷²² These factors can compound each other; the result of disruptive events may thus be attrition from the market, as a single incident becomes the tipping point at which companies decide it is no longer worth investing in continued production of a marginally profitable product, and instead decide to shift those resources elsewhere. Discontinuation of an Essential Medicine could thus even be a moneymaking business decision, as production lines are shifted to more lucrative products. In the case of the Canadian shortage of injectables that helped draw attention to this issue, a headline in the Winnipeg Free Press put it bluntly: “Drug maker could profit from own shortage”.⁷²³

hydration or irrigation. Nonetheless, the US market is dependent on three main suppliers; when one manufacturer’s facilities in Puerto Rico were hit, it did not have additional capacity it could mobilize, while its competitors were also unable to fill the gap. See e.g., Mazer-Amirshahi, Maryann & Erin R Fox. “Saline Shortages — Many Causes, No Simple Solution” (2018) 378:16 N Engl J Med 1472–1474, online: <<http://www.nejm.org/doi/10.1056/NEJMp1800347>>.

⁷²⁰ Sher, Jonathan, “IV drug bags: Made in Puerto Rico, still reeling from Hurricane Maria, the bags used in Ontario are in short supply, with hospitals working around the problem”, *The London Free Press* (16 November 2017), online: <<https://lfpres.com/2017/11/16/iv-drug-bags-made-in-puerto-rico-still-reeling-from-hurricane-maria-the-bags-used-in-ontario-are-in-short-supply-with-hospitals-working-around-the-problem/wcm/a5489fb3-fbd1-33db-c9b7-227b2905fc7b/>>.

⁷²¹ Canadian Agency for Drugs and Technologies in Health (CADTH). *Drug Supply Disruptions*, Environmental Scan, by Canadian Agency for Drugs and Technologies in Health (CADTH), Environmental Scan Issue 17 (2011).

⁷²² Acosta, Angela et al., “Medicine Shortages: Gaps Between Countries and Global Perspectives” (2019) 10 Front Pharmacol 763, online: <<https://www.frontiersin.org/article/10.3389/fphar.2019.00763/full>>.

⁷²³ Tam, Pauline. “Drug maker could profit from own shortage”, *Winnipeg Free Press* (17 March 2012), online: <<https://www.winnipegfreepress.com/canada/drug-maker-could-profit-from-own-shortage-143035585.html>>.

The company referenced in that headline is Sandoz, a company that played a key role in the injectables shortage of the early 2010s. Sandoz dominated the generic injectable market in Canada at the time, with over 80% of the market share.⁷²⁴ Their product line included old drugs like phenobarbital, an Essential Medicine first synthesized over a century before. In turn, this market dominance fuelled shortages when, in February 2012, Sandoz slowed or stopped production on nearly all its products. The ostensible problem was that the US FDA had raised concerns about the risk of contamination at its plant in Boucherville, Québec; accordingly, “Sandoz Canada responded to the warning letter by slowing down production in order to retool its Boucherville plant and by focusing on the production of its top eight drugs”.⁷²⁵ Concerningly, HESA would later hear that Health Canada first found out about these FDA concerns regarding conditions at a Canadian facility by reading the FDA website.⁷²⁶

Then, in early March, a fire broke out at the same plant.⁷²⁷ Unfortunately, these incidents proved an opportunity for Sandoz to move away from less profitable old products towards new, more lucrative ones. In his review of the injectables shortages of the early 2010s, Kaposy concludes that the Canadian “drug shortage crisis was created through a lack of governmental oversight while pharmaceutical companies left the generic injectable market and the supply of critical health resources became dependent upon a single fair-weather and profit

⁷²⁴ Media reports, like those cited elsewhere in this section, frequently said ninety percent. Kaposy, Chris. “Drugs, Money, and Power: The Canadian Drug Shortage” (2014) 11:1 *Bioethical Inquiry* 85–89, online: <<http://link.springer.com/10.1007/s11673-013-9494-z>>.

⁷²⁵ Kaposy, Chris. “Drugs, Money, and Power: The Canadian Drug Shortage” (2014) 11:1 *Bioethical Inquiry* 85–89, online: <<http://link.springer.com/10.1007/s11673-013-9494-z>>. See also Anderssen, Erin & Sean Silcoff, “Sandoz suspends some drug production after U.S. warning”, *Globe and Mail* (19 February 2012), online: <<https://www.theglobeandmail.com/life/health-and-fitness/sandoz-suspends-some-drug-production-after-us-warning/article533733/>>.

⁷²⁶ Standing Committee on Health, *Drug Supply in Canada: A Multi-Stakeholder Responsibility*, 41st Parliament, 1st Session (2012), online: <<https://www.ourcommons.ca/Content/Committee/411/HESA/Reports/RP5640047/hesarp09/hesarp09-e.pdf>> at p.2.

⁷²⁷ Mackrael, Kim, Carys Mills & Anna Mehler Paperny, “Hospitals scramble with backup plans in face of national drug shortage”, *Globe and Mail* (8 March 2012), online: <<https://www.theglobeandmail.com/news/politics/hospitals-scramble-with-backup-plans-in-face-of-national-drug-shortage/>>.

motivated friend”.⁷²⁸ Aside from providing a clear illustration of how accidents and business interests can both lead to changes in production, this story also underscores Canada’s *de facto* reliance on foreign regulatory bodies in areas like inspections, and, given FDA concerns about Canadian manufacturing facilities, the regulatory fiction that the only acceptable arbiter of appropriate drug quality is Canadian approval.

All of this also relates to a key barrier in addressing incidents of this kind, the fact that it was “difficult to quantify and determine the extent of drug shortages in Canada because manufacturers [were] not required to report disruptions in drug supply to Health Canada and because there [was] no single accountable Canadian organization that provides system-wide drug distribution oversight”.⁷²⁹ This in turn illustrates how minimal the requirements for industry reporting were a mere decade ago. The evolving response has helped demonstrate the importance of a federal role in managing drug shortages. Early in the injectables shortage, the Government of Canada eschewed any federal responsibility for drug shortages. “Rather than take a leadership role, the Prime Minister opted to avoid blame by alleging that drug supply issues are a provincial responsibility” was one assessment of Stephen Harper’s response.⁷³⁰ The Prime Minister’s views were echoed by others in the governing party; Health Minister Leona Aglukkaq said the government’s role was to assure the safety of drugs but that it had no role in supply.⁷³¹ Elsewhere, Conservative MP Kellie Leitch, a physician, echoed that “the federal government under the Constitution has no responsibility in dealing with the drug shortage problem”.⁷³² While the government encouraged pharmaceutical industry participation in a voluntary industry-run reporting website, it resisted

⁷²⁸ Kaposy, Chris. “Drugs, Money, and Power: The Canadian Drug Shortage” (2014) 11:1 Bioethical Inquiry 85–89, online: <<http://link.springer.com/10.1007/s11673-013-9494-z>>.

⁷²⁹ Canadian Agency for Drugs and Technologies in Health (CADTH). *Drug Supply Disruptions*, Environmental Scan, by Canadian Agency for Drugs and Technologies in Health (CADTH), Environmental Scan Issue 17 (2011).

⁷³⁰ Kaposy, Chris. “Drugs, Money, and Power: The Canadian Drug Shortage” (2014) 11:1 Bioethical Inquiry 85–89, online: <<http://link.springer.com/10.1007/s11673-013-9494-z>>.

⁷³¹ Duffin, Jacalyn. “Canadian drug shortage: recent history of a mystery” (2012) 184:8 CMAJ 1000.

⁷³² Kondro, Wayne. “For the record - It’s not our problem, feds say of drug shortages” (2012) 184:8 Canadian Medical Association Journal E417–E423, online: <<http://www.cmaj.ca/cgi/doi/10.1503/cmaj.109-4184>>.

mandatory reporting; the government subsequently claimed this voluntary approach was a faster and more efficient way of initiating reporting than regulations.⁷³³ In reality, such measures proved insufficient, with some companies reporting too slowly, and others not participating at all.⁷³⁴

An NDP Private Member's Bill to amend the *Department of Health Act* to require mandatory reporting of shortages was unsuccessful in 2013.⁷³⁵ In 2015, however, the government itself proposed changes to the *Food and Drug Regulations* that would make reporting mandatory.⁷³⁶ These regulations were not enacted before the Conservative government lost power. The incoming Liberal government would ultimately support similar measures, expanding manufacturer obligations to include reporting shortages.⁷³⁷ On March 14, 2017, Health Canada finally took over the reporting site from the pharmaceutical industry (the contract for the site itself went to Bell Canada), and notification became mandatory.⁷³⁸ Canada, in other words, now has a website that, in theory, offers a list of drugs in shortage, based upon obligatory participation by the pharmaceutical industry. However, such measures still do not provide a complete picture. Particularly pertinent for the purposes of this thesis, it should be noted that these requirements remain explicitly tied to a DIN (Drug Identification Number); as such, they do not apply to a drug that is not officially approved in Canada, even if that drug is regularly and widely used, and shortages impact patient care.

⁷³³ "Voluntary drug-shortage reporting adopted despite concerns", *CBC News* (27 December 2012), online: <<https://www.cbc.ca/news/health/voluntary-drug-shortage-reporting-adopted-despite-concerns-1.1156278>>.

⁷³⁴ Donelle, Jessy, Jacalyn Duffin & Jon Pipitone. *Assessing Canada's Drug Shortage Problem* (2018: CD Howe Institute).

⁷³⁵ Bill C-523 An Act to amend the Department of Health Act (disclosure of drug shortages) 1st Session, 41st Parliament.

⁷³⁶ "Regulations Amending the Food and Drug Regulations (Shortages and Discontinuation of Sale of Drugs)", *Canada Gazette* (25 June 2015), Vol. 149, No. 25.

⁷³⁷ Under the heading Shortages of Drugs and Interruption and Discontinuation of Sale of Drugs. C.01.014.7 - C.01.014.11, *Food and Drug Regulations* (C.R.C., c. 870).

⁷³⁸ Donelle, Jessy, Jacalyn Duffin & Jon Pipitone. *Assessing Canada's Drug Shortage Problem* (2018: CD Howe Institute).

Essential Medicines and shortages in Canada

The concept of Essential Medicines has informed the conversation around shortages in Canada, not least via their repeated invocation in the 2012 HESA report on shortages, which makes frequent reference to both essential medicines and medically necessary drugs, albeit – as explored elsewhere in this thesis – without formally defining either term.⁷³⁹ More importantly, this report recommends that the “Minister of Health in consultation with the provinces and territories, explore the possibility of the Canadian Agency for Drugs and Technologies in Health establishing a list of medicines supplied by only one or two companies and considered critical to medical care”.⁷⁴⁰ In other words, it recommends considering the creation of a list of medicines “critical to medical care” that are most at risk of not being available at all.⁷⁴¹ Such a list is an important counterpart to the reporting of shortages themselves. Identifying drugs that are particularly important for care before shortages actually occur can help inform other proactive, rather than reactive, responses; the same is true of drugs at particular risk of shortage. Other commentators have emphasized the broader importance of Essential Medicines in this context, even without incorporating additional risk factors such as sole-source supplies: “In terms of prevention, an Essential Medicines List (EML) is regarded as crucial” write Donelle and colleagues

⁷³⁹ Although the report uses both terms fairly indiscriminately, at one point it does refer to the Committee having “heard from a number of witnesses that critical, or medically necessary, drugs deemed to be essential and provided by only one or two suppliers”, suggesting some distinction between the concepts. Standing Committee on Health, Drug Supply in Canada: A Multi-Stakeholder Responsibility, 41st Parliament, 1st Session (2012), online: <<https://www.ourcommons.ca/Content/Committee/411/HESA/Reports/RP5640047/hesarp09/hesarp09-e.pdf>> at p.9.

⁷⁴⁰ Standing Committee on Health, Drug Supply in Canada: A Multi-Stakeholder Responsibility, 41st Parliament, 1st Session (2012), online: <<https://www.ourcommons.ca/Content/Committee/411/HESA/Reports/RP5640047/hesarp09/hesarp09-e.pdf>> at p.13. This list is akin to the drugs identified by the US FDA as “medically necessary”, explored elsewhere.

⁷⁴¹ As for practical mechanisms to access drugs during times of shortage, this report has relatively little to offer. HESA acknowledges that the “Committee was told that recent shortages have highlighted the need to modernize the SAP” but makes no specific recommendations. Standing Committee on Health, Drug Supply in Canada: A Multi-Stakeholder Responsibility, 41st Parliament, 1st Session (2012), online: <<https://www.ourcommons.ca/Content/Committee/411/HESA/Reports/RP5640047/hesarp09/hesarp09-e.pdf>> at p.9.

in their 2018 report *Assessing Canada's Drug Shortage Problem*.⁷⁴² “A national commitment to maintaining and stocking drugs on such a list helps to guarantee and protect supply,” they continue; “EMLs have proved to curb drug shortages, or are expected to do so, in several nations”.⁷⁴³

Nonetheless, supporters of the introduction of a Canadian EML have also rightly cautioned it would not be a panacea for domestic shortages: “It is clear that essential medicines lists cannot be the sole protection against global drug shortages, because access to effective medicines depends not only on their identification and national purchasing power, but also on global availability”.⁷⁴⁴ This is an important reminder both that the compilation of such a list is merely one (important) step towards improving or ensuring access, and that effective measures may require considering circumstances beyond Canada's borders. The global aspects of many of these shortages also underscore the fact that Essential Medicines are a universal issue; while different countries may have differing health priorities that would govern the precise content of a national EML, a medicine that is essential in one place is – in the absence of a superior alternative – likely to be essential for that same condition elsewhere.

Ultimately, the 2012 HESA recommendations regarding a list of critical drugs in response to shortages remain the most detailed government exploration of the issue, and also remain unfulfilled a decade later. Canada still does not have an EML, or a similar list of limited-source drugs critical for care. That said, some tools to identify medically important drugs whose shortage would impact Canadians did emerge in 2012, notably the creation of the Multi-Stakeholder Steering Committee on Drug Shortages (MSSC).⁷⁴⁵ This body includes

⁷⁴² Donelle, Jessie, Jacalyn Duffin & Jon Pipitone. *Assessing Canada's Drug Shortage Problem* (2018: CD Howe Institute).

⁷⁴³ Donelle, Jessie, Jacalyn Duffin & Jon Pipitone. *Assessing Canada's Drug Shortage Problem* (2018: CD Howe Institute).

⁷⁴⁴ Eom, Gina, Paul Grootendorst & Jacalyn Duffin. “The case for an essential medicines list for Canada” (2016) 188:17–18 CMAJ E499–E503, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.160134>>.

⁷⁴⁵ Multi-Stakeholder Steering Committee on Drug Shortages in Canada, “Protocol for the Notification and Communication of Drug Shortages” (2017), online: <https://www.drugshortagescanada.ca/files/MSSC_Protocol_2017.pdf>.

representatives from the federal and provincial governments, alongside industry and health professional associations. The MSSC is the source of the Tier 1-3 drug shortage classifications, a tool whose practical utility would be put to the test in the response to the COVID-19 pandemic. Currently, this classification system comes the closest to realizing the mooted list of at-risk critical drugs. Drawing upon the (now obligatory) reporting requirements of manufacturers, Tier 1 encompasses anticipated shortages, Tier 2 actual shortages, and Tier 3 “captures those shortages with the greatest potential impact on the Canadian drug supply and health care systems by virtue of availability of alternative supplies, ingredients or therapies”.⁷⁴⁶ As discussed shortly, the COVID-19 pandemic has drawn attention to Tier 3 shortages, and how the Tier 3 list has been used as a springboard to import medicines from unapproved sources during the pandemic via interim order by the Minister of Health. However, even this application of the Tier 3 list raises questions about how similar tools could be utilized more effectively. For instance, Tier 3 status, on its own, does little but emphasize the need for communication between the stakeholders.⁷⁴⁷ Only by applying this list in a regulatory context like a special path for importation does it assert a more active role in addressing shortages. More broadly, although the Tier 3 list does on occasion include drugs at risk of shortage – the precise reasons for when or why an anticipated shortage would be listed in Tier 3 remain opaque – it remains largely a reactive tool. Rather than add particular drugs in response to an actual or anticipated shortage, a stronger list would publicly identify drugs of medical importance even in the absence of imminent risk, especially where they have characteristics – such as small markets or single suppliers – that increase the risk of shortages in the future. While such a list would not be identical to a Canadian EML, constructing it with explicit reference to a Canadian EML, and in turn the WHO MEML, would be a useful step. This would be illustrated by the COVID-19 pandemic.

⁷⁴⁶ Multi-Stakeholder Steering Committee on Drug Shortages in Canada, “Protocol for the Notification and Communication of Drug Shortages” (2017), online: <https://www.drugshortagescanada.ca/files/MSSC_Protocol_2017.pdf>.

⁷⁴⁷ Multi-Stakeholder Steering Committee on Drug Shortages in Canada, “Protocol for the Notification and Communication of Drug Shortages” (2017), online: <https://www.drugshortagescanada.ca/files/MSSC_Protocol_2017.pdf>.

COVID-19: Lessons from a pandemic

This thesis was written against the backdrop of the SARS-CoV-2 pandemic. Putting aside any dubiously humorous remarks about social distancing as a measure for public health protection and thesis completion alike, the pandemic has served to drive home a number of the issues under discussion. Most broadly, it serves to further underscore the fact that global health is indeed global, and that events in Canada will inevitably be shaped by outside influences, from novel pathogens arriving from abroad, to drugs from abroad that fail to arrive. More particularly, the pandemic has also shone a spotlight on the importance of ongoing access to off-patent Essential Medicines. Of the treatments (and purported treatments) that gained popularity during the pandemic, particularly during the period prior to the introduction of vaccines as the primary pharmaceutical intervention, only a relatively small number were still under patent.⁷⁴⁸ Instead, especially during those early months of the response, it was old, off-patent Essential Medicines that dominated the discussion of COVID-19 prophylaxis, treatment and cure.⁷⁴⁹ Indeed, given there were no approved drugs for this novel pathogen at the beginning of the pandemic, all pharmaceutical interventions were initially off-label uses of medicines for other conditions.⁷⁵⁰ The most successful drug employed for COVID-19 care for much of this period, the corticosteroid dexamethasone, is an off-patent Essential Medicine developed in the 1960s.⁷⁵¹ More recently, one of the first

⁷⁴⁸ This short list includes including remdesivir and some monoclonal antibodies such as bamlanivimab. The number has subsequently increased, including drugs like molnupiravir and Paxlovid. In turn, intellectual property rights are a larger concern for global access to these novel, patented drugs than the off-patent drugs in this thesis. See e.g., Usher, Ann Danaiya, "The global COVID-19 treatment divide" (2022) 399:10327 *The Lancet* 779–782, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673622003725>>.

⁷⁴⁹ Hossen, Md Shafiul et al., "A Review on Current Repurposing Drugs for the Treatment of COVID-19: Reality and Challenges" (2020) 2:10 *SN Compr Clin Med* 1777–1789, online: <<http://link.springer.com/10.1007/s42399-020-00485-9>>; Zhou, Yuyong et al., "In vitro efficacy of artemisinin-based treatments against SARS-CoV-2" (2021) 11:1 *Sci Rep* 14571, online: <<http://www.nature.com/articles/s41598-021-93361-y>>.

⁷⁵⁰ See e.g., Singh, Thakur Uttam et al., "Drug repurposing approach to fight COVID-19" (2020) *Pharmacol Rep* 72:6 1479–1508. This article underscores the role of off-label prescribing, but also illustrates the importance of clinical trials for completely novel uses of old drugs.

⁷⁵¹ See e.g., Tomazini, Bruno M et al., "Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial" (2020) 324:13 *JAMA* 1307, online:

effective treatments for the virus itself, Pfizer's combination drug Paxlovid, has straddled old and new, combining the novel drug nirmatrelvir with the off-patent Essential Medicine ritonavir, long in use for the treatment of HIV.⁷⁵² The off-patent Essential Medicines that have attracted the most attention, however, have quite disproportionately been drugs originally used for Neglected Diseases.

The first to attain notoriety was hydroxychloroquine, touted by heads of state from American President Donald Trump to Brazilian President Jair Bolsonaro as a miracle cure for COVID-19.⁷⁵³ Both it and the related drug chloroquine are long-established Essential Medicines. Originally antimalarials, both have also been previously repurposed for other indications, some of which are themselves found on the WHO MEML, such as the treatment of the autoimmune disease lupus. Despite the hype, however, they were ultimately shown not to be effective for COVID-19.⁷⁵⁴ Trump, among others, also pushed azithromycin, another Essential Medicine with numerous indications including Neglected Diseases like trachoma and yaws.⁷⁵⁵ Still other Essential Medicines for Neglected Diseases, already encountered at length in this thesis, have also had their moment as purported pandemic wonder drugs. For instance, continuing the presidential theme, Madagascar's President Andry Rajoelina personally promoted Covid Organics, an unproven tonic (and later capsule) derived primarily from *Artemisia*, the same

<<https://jamanetwork.com/journals/jama/fullarticle/2770277>>; Asselah, Tarik et al., "COVID-19: Discovery, diagnostics and drug development" (2021) 74:1 J Hepatol 168–184.

⁷⁵² See e.g., Mahase, Elisabeth, "Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports" (2021) BMJ n2713, online:

<<https://www.bmj.com/lookup/doi/10.1136/bmj.n2713>>; Hammond, Jennifer et al., "Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19" (2022) N Engl J Med NEJMoa2118542, online: <<http://www.nejm.org/doi/10.1056/NEJMoa2118542>>.

⁷⁵³ Berlivet, Luc & Ilana Löwy, "Hydroxychloroquine Controversies: Clinical Trials, Epistemology, and the Democratization of Science" (2020) 34:4 Med Anthropol Q 525–541.

⁷⁵⁴ See e.g., Self, Wesley H et al., "Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial" (2020) 324:21 JAMA 2165, online: <<https://jamanetwork.com/journals/jama/fullarticle/2772922>>;

National Institutes of Health COVID-19 Treatment Guidelines Panel, "Coronavirus Disease 2019 (COVID-19) Treatment Guidelines" (8 July 2021 version), online:

<<https://www.covid19treatmentguidelines.nih.gov/>>.

⁷⁵⁵ Unlike many of the Neglected Disease drugs discussed herein, azithromycin has many indications beyond Neglected Diseases, and is widely prescribed in HICs. Niburski, Kacper & Oskar Niburski, "Impact of Trump's Promotion of Unproven COVID-19 Treatments on Social Media and Subsequent Internet Trends: Observational Study" (2020) 22:11 J Med Internet Res e20044, online: <<http://www.jmir.org/2020/11/e20044/>>.

genus of plants that gave the world artemisinin, both domestically and throughout Africa.⁷⁵⁶ Artesunate, meanwhile, has itself been under examination, including as part of the Solidarity trial, a large WHO trial for potential COVID-19 treatments (a previous round of which was among trials concluding hydroxychloroquine was ineffective).⁷⁵⁷

Another drug attaining and perhaps even surpassing the popularity and politicization of hydroxychloroquine is ivermectin.⁷⁵⁸ In one inauspicious moment (among many) for evidence-based policy during the pandemic, a number of Latin American countries changed their COVID-19 treatment guidelines to include ivermectin on the basis of an unreviewed preprint originating from Surgisphere, a subsequently disgraced US company forced to retract high-profile COVID-19 papers in both *The Lancet* and *The New England Journal of Medicine* after falsifying their data for studies of other drugs for COVID-19.⁷⁵⁹ Subsequent studies favourable to ivermectin have also been discredited, though its proponents have refused to disappear as of this writing.⁷⁶⁰ This thesis will not wade deeper into the quagmire of the promotion and politicization of drugs like ivermectin and hydroxychloroquine.⁷⁶¹ It will also not linger on other emerging legal issues around

⁷⁵⁶ Bosha, Sarah L & Adam R Houston, "The dangers of playing politics with COVID-19 cures", (8 December 2020), online: *African Arguments* <<https://africanarguments.org/2020/12/the-dangers-of-playing-politics-with-covid-19-cures/>>.

⁷⁵⁷ Ledford, Heidi, "International COVID-19 trial to restart with focus on immune responses" (2021) *Nature* d41586-021-01090-z, online: <<http://www.nature.com/articles/d41586-021-01090-z>>. See also Zhou, Yuyong et al., "In vitro efficacy of artemisinin-based treatments against SARS-CoV-2" (2021) 11:1 *Sci Rep* 14571, online: <<http://www.nature.com/articles/s41598-021-93361-y>>. As of the submission of this thesis, no definitive conclusion had been reached, though there is also little sign of it becoming a breakthrough cure.

⁷⁵⁸ Lind, Jennifer N et al., "Increase in Outpatient Ivermectin Dispensing in the US During the COVID-19 Pandemic: A Cross-Sectional Analysis" (2021) 36:9 *J Gen Intern Med* 2909–2911, online: <<https://link.springer.com/10.1007/s11606-021-06948-6>>.

⁷⁵⁹ Mega, Emiliano Rodríguez, "Latin America's embrace of an unproven COVID treatment is hindering drug trials" (2020) 586:7830 *Nature* 481–482; Reardon, Sara, "Flawed ivermectin preprint highlights challenges of COVID drug studies" (2021) 596:7871 *Nature* 173–174; Ledford, Heidi & Richard Van Noorden, "High-profile coronavirus retractions raise concerns about data oversight" (2020) 582:7811 *Nature* 160.

⁷⁶⁰ See e.g., Reardon, Sara, "Flawed ivermectin preprint highlights challenges of COVID drug studies" (2021) 596:7871 *Nature* 173–174; Jarry, Jonathan, "The Ivermectin Train Cannot Stop", (30 October 2021), online: *McGill Office for Science and Society* <<https://www.mcgill.ca/oss/article/covid-19/ivermectin-train-cannot-stop>>.

⁷⁶¹ The politicization of these drugs is already a matter of academic inquiry. See e.g., Barnett, Michael L et al., "Association of County-Level Prescriptions for Hydroxychloroquine and Ivermectin

these off-patent Essential Medicines for Neglected Diseases, such as legal actions seeking to require care providers to provide unproven treatments to patients.⁷⁶² It is also perhaps little surprise that at a time when hucksters were pushing repurposed old malaria medicines like hydroxychloroquine, Martin Shkreli himself would briefly resurface, requesting to be released from prison in order to “assist in research work on COVID-19”.⁷⁶³ His request was rejected, with the judge characterizing his claims around developing a cure for COVID-19 as “delusional self-aggrandizing behavior”.⁷⁶⁴ Long story short: none of the most aggressively and partisanly promoted old Essential Medicines for Neglected Diseases have thus far proven effective for COVID-19.

Nonetheless, this is the most high-profile attention many of these drugs have received, especially in high-income countries, in a very long time.⁷⁶⁵ These Essential (albeit not for COVID-19) Medicines also pose an interesting what-if scenario: Imagine for a minute the scandal that would have erupted under a slightly different set of circumstances, where the Essential Medicine that proved an effective treatment was one not marketed at all, especially in a country with ready resources to afford it. Ivermectin has been available in Canada for only a few years; regardless of its ultimate effectiveness for COVID-19, it would have been an even greater political fiasco if Canada lacked formal access to a (purported) treatment

With County-Level Political Voting Patterns in the 2020 US Presidential Election” (2022) JAMA Intern Med, online:

<<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2789363>>. For another interesting discussion of the political aspect, see Lasco, Gideon & Vincen Gregory Yu, “Pharmaceutical messianism and the COVID-19 pandemic” (2021) Social Science & Medicine 114567, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0277953621008996>>.

⁷⁶² A number of legal actions have been taken against hospitals in multiple U.S. states to require the provision of ivermectin. See e.g., Bard, Jennifer, “Legal and Ethical Analysis of Court-Ordered Ivermectin Treatment for COVID-19”, (2 September 2021), online: *Bill of Health (Harvard Law)* <<https://blog.petrieflom.law.harvard.edu/2021/09/02/court-ordered-ivermectin-covid/>>; Ebert, Alex & Allie Reed, “String of Suits Force Covid-19 Ivermectin Treatment in Hospitals”, *Bloomberg Law* (1 September 2021), online: <<https://news.bloomberglaw.com/health-law-and-business/string-of-suits-force-covid-19-ivermectin-treatment-in-hospitals>>.

⁷⁶³ Shkreli, Martin et al. “In silico screening for potential COVID-19 beta-coronavirus non-nucleoside RdRp inhibitors” Preprint, online: <<https://prosperopharma.com/covid19.pdf>>.

⁷⁶⁴ “‘Delusional’ Martin Shkreli denied prison release by judge”, *AP News* (17 May 2020), online: <<https://apnews.com/af8459fd4e1d7a36e985b3933827ff54>>.

⁷⁶⁵ On an autoethnographical note, when discussing his work, this author no longer finds himself explaining what ivermectin is, even if he still has to emphasize its importance to global health.

widely available elsewhere, even if that treatment were off-label.⁷⁶⁶ Were artesunate proven to be useful, Canada would still lack even off-label access. And as noted earlier, chloroquine, in shortage even before the pandemic, was ultimately discontinued by the sole remaining source in Canada in July of 2021. Perhaps COVID-19 might have revived chloroquine's fortunes had it proven effective; on the other hand, perhaps the same factors that led to shortages before the pandemic would have impeded effective access to it for COVID-19.

Regardless of their ultimate utility for COVID-19, the scramble for repurposed drugs also serves as an important bridge between the specific issues facing off-patent Essential Medicines for Neglected Diseases and the broader issues of shortages and global supply chains. Broadly speaking, shortages during the pandemic were driven by two elements in particular: a surge in demand (both foreign and domestic), and disruption of the supply chain.⁷⁶⁷ Increased demand as part of the COVID-19 response – whether based on sound scientific evidence or driven by hype, and whether for actual use or simply stockpiling – led to serious shortages for patients who depend on these Essential Medicines for other conditions all over the world. For instance, a run on hydroxychloroquine posed real

⁷⁶⁶ This did occur elsewhere, illustrating the unpredictability of access to some Essential Medicines outside HICs as well. At the start of the pandemic, ivermectin was not marketed for human use in South Africa. Initially, it was accessible only via a Controlled Compassionate Use Programme managed by the South African Health Products Regulatory Authority (SAHPRA). However, by apparent coincidence, in March of 2021, a backlog of pharmaceutical applications was cleared, permitting the marketing of a rosacea cream containing ivermectin. The presence of a product containing ivermectin as an active ingredient opened the door to compounding (which in South Africa requires the underlying drug to be marketed first). The details of these two routes to access were further set out in a court order, made in settlement of a series of cases brought against SAHPRA and the Ministry of Health over ivermectin access. See e.g., Abdool Karim, Aisha & Joan van Dyk, "Farmers vs pharmacists: How South Africa's ivermectin use slips through the cracks", *Daily Maverick* (8 November 2021), online: <<https://www.dailymaverick.co.za/article/2021-11-08-farmers-vs-pharmacists-how-south-africas-ivermectin-use-slips-through-the-cracks/>>; South African Health Products Regulatory Authority, "SAHPRA Statement - High Court Order - Ivermectin", (9 April 2021), online: <<https://www.sahpra.org.za/news-and-updates/sahpra-statement-high-court-order-ivermectin/>>.

⁷⁶⁷ Gaudette, Étienne, "COVID-19's Limited Impact on Drug Shortages in Canada" (2020) 46:s3 Canadian Public Policy S307–S312, online: <<https://utpjournals.press/doi/10.3138/cpp.2020-107>>.

risks for patients with lupus.⁷⁶⁸ Meanwhile, ivermectin shortages have transcended the species barrier, with veterinary supplies depleted by human demand.⁷⁶⁹ Compounding the situation, increased demand met a disrupted supply. China and India are today the primary sources of APIs as well as many finished drugs.⁷⁷⁰ China's production was initially hit hard by the virus; while it recovered fairly quickly, this nonetheless affected exports, which in turn faced further pandemic-related logistical barriers elsewhere in their international journey at a time when many countries shut their borders to varying degrees.⁷⁷¹ By contrast with these indirect barriers, India initially placed specific legal restrictions on exports of both API and finished products for drugs like hydroxychloroquine thought to be important in the pandemic response in order to protect its presumed domestic needs.⁷⁷² This phenomenon was not restricted solely to lynchpin manufacturing countries; other countries like the UK also banned exports of drugs thought to be useful for COVID-19, including hydroxychloroquine and chloroquine.⁷⁷³ Thus, the pandemic disrupted manufacturing sites; border closures and similar measures disrupted international transport; countries banned or restricted exports of both ingredients and finished drugs; and demand increased for certain drugs (through both use and stockpiling), creating shortages for patients requiring Essential

⁷⁶⁸ Peschken, Christine A, "Possible Consequences of a Shortage of Hydroxychloroquine for Patients with Systemic Lupus Erythematosus amid the COVID-19 Pandemic" (2020) 47:6 J Rheumatol 787–790, online: <<http://www.jrheum.org/lookup/doi/10.3899/jrheum.200395>>.

⁷⁶⁹ See e.g., Little, Simon & Kylie Stanton, "People seeking horse dewormer as COVID-19 'cure' creates shortage, says B.C. livestock supplier", *Global News* (1 September 2021), online: <<https://globalnews.ca/news/8160269/people-seeking-horse-dewormer-as-covid-19-cure-creating-shortage-in-b-c-says-livestock-supplier/>>; Milman, Oliver, "US horse owners face ivermectin shortage as humans chase unproven Covid 'cure'", *The Guardian* (20 September 2021), online: <<https://www.theguardian.com/world/2021/sep/20/ivermectin-shortage-horse-owners-covid>>.

⁷⁷⁰ Elbeddini, Ali, Naushin Hooda & Lucy Yang, "Role of Canadian pharmacists in managing drug shortage concerns amid the COVID-19 pandemic" (2020) 153:4 Can Pharm J 198–203, online: <<http://journals.sagepub.com/doi/10.1177/1715163520929387>>.

⁷⁷¹ See e.g., "China's API makers restart manufacturing, but logistics disruptions hinder shipping", *Global Times* (25 March 2020), online: <<https://www.globaltimes.cn/content/1183692.shtml>>.

⁷⁷² See e.g., Silverman, Ed, "India bans exports of drug touted by Trump as potential Covid-19 treatment", *STAT News* (25 March 2020), online: <<https://www.statnews.com/pharmalot/2020/03/25/india-trump-hydroxychloroquine-coronavirus-covid19/>>.

⁷⁷³ "UK bans parallel export and hoarding of three Covid-19 drugs", *GlobalData Healthcare* (13 March 2020), online: <<https://www.pharmaceutical-technology.com/comment/parallel-export-covid-19/>>.

Medicines for their usual indications. Supply issues, occurring for some or all of these reasons, have been observed in many countries during the pandemic.⁷⁷⁴ In Canada, these elements of increased demand and decreased availability exacerbated pre-existing issues with the drug supply, particularly for off-patent Essential Medicines, and including those for Neglected Diseases.⁷⁷⁵

Although Canada does not have an Essential Medicines List, the pandemic has drawn more attention to an existing list of drugs that comes into play for shortages of particular concern. As noted earlier, Canada maintains a list of medicines in Tier 3 shortage, which are “those that have the greatest potential impact on Canada’s drug supply and healthcare system”.⁷⁷⁶ Tier 3 shortages increased considerably as a result of the pandemic; Health Canada has noted that 45 Tier 3 shortages were experienced in 2020, compared to just 10 in 2019.⁷⁷⁷ As might be imagined, a sizeable majority of the drugs on the Tier 3 list during the pandemic – though certainly not all – are used directly in the COVID-19 response.⁷⁷⁸ This includes drugs not merely for treatment of the virus itself, but those used to care for patients in other ways, such as sedatives and pain medications used when intubating patients; in some instances, patients with COVID-19 consumed such drugs “at double or triple the rate of other intensive care patients”.⁷⁷⁹ The precise drugs in shortage changed over time; for instance,

⁷⁷⁴ Socal, Mariana P, Joshua M Sharfstein & Jeremy A Greene, “The Pandemic and the Supply Chain: Gaps in Pharmaceutical Production and Distribution” (2021) 111:4 Am J Public Health 635–639.

⁷⁷⁵ Gaudette, Étienne, “COVID-19’s Limited Impact on Drug Shortages in Canada” (2020) 46:s3 Canadian Public Policy S307–S312, online: <<https://utpjournals.press/doi/10.3138/cpp.2020-107>>; Elbeddini, Ali, Naushin Hooda & Lucy Yang, “Role of Canadian pharmacists in managing drug shortage concerns amid the COVID-19 pandemic” (2020) 153:4 Can Pharm J 198–203, online: <<http://journals.sagepub.com/doi/10.1177/1715163520929387>>.

⁷⁷⁶ Health Canada, “Tier 3 Drug Shortages”, online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/covid19-interim-order-drugs-medical-devices-special-foods/information-provisions-related-drugs-biocides/tier-3-shortages.html>>.

⁷⁷⁷ Health Canada, “Explanatory note: Interim order No. 2 extends measures for drugs, medical devices and foods for a special dietary purpose” (8 March 2021) online:

<<https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drug-medical-device-food-shortages/interim-order-2021/explanatory-note.html>>.

⁷⁷⁸ Basky, Greg, “Temporary fixes to chronic drug shortages leave Canada vulnerable” (2020) 192:31 CMAJ E898–E899.

⁷⁷⁹ Basky, Greg, “Temporary fixes to chronic drug shortages leave Canada vulnerable” (2020) 192:31 CMAJ E898–E899.

hydroxychloroquine appeared on the list early in the pandemic, then was subsequently removed as evidence around its utility evolved and global production and consumption patterns shifted.⁷⁸⁰

As an example of the early impact of the pandemic on off-patent Essential Medicines in general, consider the version of the list dated June 10, 2020, when there were 30 drugs in Tier 3 shortage.⁷⁸¹ Of these 30, only two were developed in the 21st Century; the oldest, morphine, dates back more than two centuries.⁷⁸² Two thirds of these drugs were on the WHO MEML. Even more concerning, four of the drugs listed as being in Tier 3 shortage – three of which (atracurium, vecuronium, and propylthiouracil) are also on the WHO MEML – had no manufacturer authorized to market the drug in Canada at the time. In all four cases, Health Canada's Drug Product Database shows that every company ever approved to sell the drug in Canada had discontinued the product before COVID-19 first appeared. In other words, four of the drugs identified by Health Canada early in the pandemic as among “those that have the greatest potential impact on Canada's drug supply and healthcare system”, including three Essential Medicines, were already unavailable on the Canadian market before the pandemic began.

Both atracurium and vecuronium (along with the only non-WHO MEML drug of the four, pancuronium) were specifically categorized on Health Canada's Tier 3 List as being for use in the COVID-19 response. This is because all three were used as part of putting COVID-19 patients on ventilators, a process that is especially difficult and painful in the absence of appropriate drugs. It is worth noting that not all these drugs would necessarily be the first choice for this role under normal circumstances – atracurium has been informally described to the author as one step removed from a poisoned arrow – but during a pandemic, when demand increases and supply may be impacted, the value of having a fully stocked

⁷⁸⁰ Hydroxychloroquine was added to the list on March 23/2020; it was no longer present as of May 15/2020. Copies in author's possession.

⁷⁸¹ See also Houston, Adam R, “New Tricks for Old Drugs? Canada must change how it accesses Essential Medicines”, *Healthy Debate* (23 June 2020), online: <https://healthydebate.ca/opinions/accesses-essential-medicines>.

⁷⁸² Huxtable, R J & S K Schwarz, “The isolation of morphine--first principles in science and ethics” (2001) 1:4 *Mol Interv* 189–191

medicine cabinet becomes readily apparent. The fourth drug, propylthiouracil, is an Essential Medicine used for treating pregnant women with hyperthyroidism; its Canadian discontinuation in 2019 did not affect the COVID-19 response but raised alarm bells in the medical community in its own right.⁷⁸³ The key point, once again, is that Canada entered the pandemic without any formal access at all to four drugs subsequently classified as having the “greatest potential impact” on Canada’s health system. Although Health Canada had no way of predicting a sudden surge in demand or disruptions to global supply chains resulting from a nearly unprecedented pandemic of a novel disease, it could and should have identified the risk inherent in having a drug – particularly an Essential Medicine – being completely discontinued from the Canadian market. Self-evidently, this should be a serious concern even in the absence of a pandemic.

The importance of preventing shortages is even further underscored by another drug on the Tier 3 list at this time. This is the off-patent Essential Medicine that has been the most valuable in the COVID-19 response, the corticosteroid dexamethasone, which has been on the WHO MEML since the original list in 1977.⁷⁸⁴ In June of 2020, an influential pre-print – fortunately one that panned out – was published indicating dexamethasone was effective in the treatment of patients with COVID-19.⁷⁸⁵ By this time, however, it had already been on Health Canada’s Tier 3 list since May 1st for non-COVID-19 indications.⁷⁸⁶ As such, even though it is marketed in Canada, Canada was already facing shortages of this

⁷⁸³ White, Jacob, “Shortage of drug puts some pregnant women at risk”, *Healthy Debate* (10 June 2020), online: <<https://healthydebate.ca/2020/06/topic/shortage-drug-pregnant-woman-risk>>.

⁷⁸⁴ As an aside, it is worth noting that dexamethasone use for COVID-19 actually *does* implicate a use for ivermectin, in cases of co-infection with a Neglected Disease. While generally a safe drug, in patients already infected with the Neglected Disease strongyloidiasis, dexamethasone’s immunosuppressive effects can lead to hyperinfection. As such, in high-risk patient groups, even presumptive treatment with ivermectin may be appropriate. Olivera, Mario J, “Dexamethasone and COVID-19: Strategies in Low- and Middle-Income Countries to Tackle Steroid-Related Strongyloides Hyperinfection” (2021) 104:5 *The American Journal of Tropical Medicine and Hygiene* 1611–1612, online: <<https://www.ajtmh.org/view/journals/tpmd/104/5/article-p1611.xml>>.

⁷⁸⁵ Horby, Peter et al., *Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report*, preprint, by Peter Horby et al., DOI.org (Crossref), preprint (Infectious Diseases (except HIV/AIDS), 2020); subsequently published as The RECOVERY Collaborative Group, “Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report” (2020) *N Engl J Med* NEJMoa2021436, online: <<http://www.nejm.org/doi/10.1056/NEJMoa2021436>>.

⁷⁸⁶ List in author’s possession.

Essential Medicine even before it became recognized domestically as a key tool for COVID-19.⁷⁸⁷

Meanwhile, other Essential Medicines found among the 30 drugs on the Tier 3 list, such as meropenem and azithromycin, that were then being employed as part of the COVID-19 response – whether or not they were ultimately effective for that purpose – also have WHO MEML indications for Neglected Diseases.⁷⁸⁸ Still other drugs on the Tier 3 list at the time may have had less direct connections to the pandemic response, but their overall medical importance, and the risks caused by shortages, are not diminished by this fact. For instance, another Essential Medicines in Tier 3 shortage on June 10, 2020, was ethambutol, a cornerstone of tuberculosis treatment that, while marketed in Canada, boasts a history of serious shortages that have yet to be properly addressed.⁷⁸⁹ Whatever their use, the preponderance of off-patent Essential Medicines on Canada’s Tier 3 shortage list during a pandemic underscores their continued utility alongside their precariousness when it comes to sustainable access.

The COVID-19 pandemic also demonstrates that, when so moved, the Government of Canada is in fact capable of acting quickly to remedy deficiencies in the regulatory system in order to address the issue of vital medicines being unavailable on the Canadian market. On March 30, 2020, Canadian Health Minister Patty Hajdu issued an “Interim Order Respecting Drugs, Medical Devices and Foods for a Special Dietary Purpose in Relation to COVID-19” under the *Food and Drugs Act*.⁷⁹⁰ As outlined in the accompanying explanatory note, this order introduced “measures for drugs, medical devices, and foods for special dietary purposes that

⁷⁸⁷ Silverman, Ed, “Hospitals see shortages of a cheap steroid that one study says helps Covid-19 patients”, *STAT News* (25 June 2020), online: <<https://www.statnews.com/pharmalot/2020/06/25/covid19-coronavirus-dexamethasone-shortages/>>.

⁷⁸⁸ Meropenem is indicated for MDR-TB; azithromycin has indications for multiple Neglected Diseases, including trachoma and yaws.

⁷⁸⁹ See e.g., Glanz, Melanie, “Shortage of critical TB, lung infection drug worries patient, doctor”, *CBC News* (7 July 2015), online: <<https://www.cbc.ca/news/health/shortage-of-critical-tb-lung-infection-drug-worries-patient-doctor-1.3142285>>.

⁷⁹⁰ Interim Order Respecting Drugs, Medical Devices and Foods for a Special Dietary Purpose in Relation to COVID-19 (30 March 2020), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/covid19-interim-order-drugs-medical-devices-special-foods.html>>.

are necessary to help prevent or alleviate the effects of shortages directly or indirectly related to COVID-19” including their exceptional importation and sale.⁷⁹¹ This order was replaced in March 2021 by a second interim order along similar lines.⁷⁹² Both make reference to another list, the “List of Drugs for Exceptional Importation and Sale”, which is itself derived directly from the Tier 3 list.⁷⁹³ However, inclusion on the List of Drugs for Exceptional Importation and Sale requires an additional step; presence on the Tier 3 list is a prerequisite for application, but an application must nonetheless be made. Under the interim orders, importers – not the pharmaceutical companies that would apply for market approval under normal circumstances, but third parties selling those drugs – can apply to import a drug found on the Tier 3 list from an unapproved source; in turn, it can be added to the List of Drugs for Exceptional Importation and Sale.⁷⁹⁴

In between the two versions of this order, the Minister of Health issued an additional interim order in October of 2020, this time “respecting the prevention and alleviation of shortages of drugs in relation to COVID-19”. This order obliges a “person who sells a drug” to provide information upon request of the Minister, where such a request is made when the Minister has reasonable grounds to believe that there is a shortage, or a risk of a shortage, that is caused or exacerbated, directly or indirectly, by COVID-19, and the shortage poses or could pose a risk to human health.⁷⁹⁵ The time limit for providing the requested information “cannot be

⁷⁹¹ Interim Order Respecting Drugs, Medical Devices and Foods for a Special Dietary Purpose in Relation to COVID-19 (30 March 2020), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/covid19-interim-order-drugs-medical-devices-special-foods.html>>.

⁷⁹² Interim Order No. 2 Respecting Drugs, Medical Devices and Foods for a Special Dietary Purpose in Relation to COVID-19 (1 March 2021) online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drug-medical-device-food-shortages/interim-order-2021.html>>.

⁷⁹³ Health Canada, “List of drugs for exceptional importation and sale”, online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/covid19-interim-order-drugs-medical-devices-special-foods/information-provisions-related-drugs-biocides/list.html>>.

⁷⁹⁴ Health Canada, “Exceptional importation and sale of drugs in relation to COVID-19: For industry”, online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/covid19-interim-order-drugs-medical-devices-special-foods/information-provisions-related-drugs-biocides/industry.html>>.

⁷⁹⁵ Art. 2(1), Interim Order respecting the prevention and alleviation of shortages of drugs in relation to COVID-19 (16 October 2020), online: <<https://www.canada.ca/en/health->

less than 24 hours after the request is made unless the Minister has reasonable grounds to believe that there is a serious and imminent risk of injury to human health”.⁷⁹⁶ While the order itself imparts little sense of what the Minister would actually do with such information in practice, it stands in stark contrast to a decade before, when the federal government of the day denied having any responsibility to tackle drug shortages at all.⁷⁹⁷

In mid-April of 2021, Canada took another step to tackle drug shortages, establishing a temporary Critical Drug Reserve managed by the government itself and holding a 3-month stockpile of drugs necessary for the COVID-19 response.⁷⁹⁸ Of the initial twelve drugs included in the stockpile, eight were off-patent Essential Medicines. Little additional information emerged about this stockpile following the initial announcement, and the drugs included in the stockpile remained unchanged from its inception until it was discontinued in the summer of 2022. Nonetheless, establishing a short-term buffer to ensure important medicines are available in Canada when needed further demonstrates that the government is entirely capable of taking an active role in the drug supply to not only alleviate but prevent acute shortages.⁷⁹⁹ Furthermore, the fact its initial one year term was beyond its initially scheduled expiry suggests some decision makers believed it had merit.⁸⁰⁰

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canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/interim-order-drug-shortages.html>.

⁷⁹⁶ Art. 2(2), Interim Order respecting the prevention and alleviation of shortages of drugs in relation to COVID-19 (16 October 2020), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/interim-order-drug-shortages.html>>.

⁷⁹⁷ Kondro, Wayne. “For the record - It’s not our problem, feds say of drug shortages” (2012) 184:8 Canadian Medical Association Journal E417–E423, online: <<http://www.cmaj.ca/cgi/doi/10.1503/cmaj.109-4184>>.

⁷⁹⁸ Health Canada, “Government of Canada establishes Critical Drug Reserve to bolster Canada’s supply of drugs used to treat COVID-19”, (14 April 2021), online: <<https://www.canada.ca/en/health-canada/news/2021/04/government-of-canada-establishes-critical-drug-reserve-to-bolster-canadas-supply-of-drugs-used-to-treat-covid-19.html>>.

⁷⁹⁹ Canada does have other existing stockpiles, some of which will be revisited; most famous is the National Emergency Stockpile System (NESS), which received criticism during the pandemic, especially around personal protective equipment (PPE). See e.g., Laing, Scott & Ellen Westervelt, “Canada’s National Emergency Stockpile System: time for a new long-term strategy” (2020) 192:28 CMAJ E810–E811, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.200946>>.

⁸⁰⁰ Health Canada, “The Critical Drug Reserve during COVID-19”, online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/critical-drug-reserve.html>>, accessed April 30, 2022.

A more lasting impact of COVID-19 may be that many of the rules around importation contained in the interim orders of March 2020 and 2021 were made permanent in September of 2021, via formal changes to the *Food and Drug Regulations*.⁸⁰¹ Per the accompanying regulatory impact assessment statement (RIAS), this permanent regulatory enshrinement recognizes the longstanding need for changes that were finally catalyzed by the pandemic:

The option of allowing interim orders addressing therapeutic product shortages to expire was considered. This option was rejected because the *Food and Drug Regulations* [...], in their current state, do not have effective shortage mitigation measures for drugs and medical devices [...]. The need for these types of provisions had been recognized prior to the pandemic, and they have proven to be highly useful since the implementation of the interim orders.⁸⁰²

An analysis of the interim measures suggests that they met with some success in decreasing shortages of off-patent medicines once enacted.⁸⁰³ These steps to permanently enshrine elements of the COVID-19 response also show that the pandemic has drawn the government's attention to the broader problem of drug shortages, and in doing so, at least indirectly, to off-patent Essential Medicines. Furthermore, they recognize the inadequacy of Canada's pre-pandemic regulatory regime, even if these now-permanent measures address only a small portion of those inadequacies. None of these measures are an attempt to tackle the broader underlying problems that led to shortages in the first place. They are, however, a starting place. Increased attention to the Tier 3 list, and its practical application via

⁸⁰¹ "Regulations Amending Certain Regulations Concerning Drugs and Medical Devices (Shortages): SOR/2021-199," Canada Gazette, Part II, Volume 155, Number 18 (01 September 2021), online: <<https://www.gazette.gc.ca/rp-pr/p2/2021/2021-09-01/html/sor-dors199-eng.html>>.

⁸⁰² "Regulations Amending Certain Regulations Concerning Drugs and Medical Devices (Shortages): SOR/2021-199," Canada Gazette, Part II, Volume 155, Number 18 (01 September 2021), online: <<https://www.gazette.gc.ca/rp-pr/p2/2021/2021-09-01/html/sor-dors199-eng.html>>.

⁸⁰³ Lau, Brian et al, "COVID-19 and the prevalence of drug shortages in Canada: a cross-sectional time-series analysis from April 2017 to April 2022" (2022) 194:23 CMAJ E801–E806, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.212070>>.

the List of Drugs for Exceptional Importation and Sale, illustrate once more how a list of medicines can be valuable as an explicit regulatory point of reference. At the same time, the largely reactive nature of this list demonstrates how a pre-existing list of important medicines, in place well before a drug is in shortage (or vanishes from the market completely) might be a more valuable tool, and at minimum a complementary one.

Something else that Canada recognizes in its recent regulatory changes is that Canada is not alone in revisiting issues around its drug supply as a consequence of COVID-19:

Finally, the option of allowing these powers to expire would not align with the approach taken by other countries. Countries including the United States, the United Kingdom, Ireland, France, Japan, and Australia have taken lessons learned from the pandemic into consideration and are developing partnerships, regulatory frameworks, and other long-term solutions to address shortages of key therapeutic products.⁸⁰⁴

As but one example, the pandemic has helped advance the concept of an Essential Medicines List, at least in some form, in unlikely quarters. In August of 2020, U.S. President Donald Trump issued an executive order requiring a list of “essential medicines” be compiled with 90 days.⁸⁰⁵ The resulting list was released by the US FDA on October 30, 2020.⁸⁰⁶ The list feeds into the broader goal reflected in the title of the order: “Combating Public Health Emergencies and Strengthening National Security by Ensuring Essential Medicines, Medical Countermeasures, and

⁸⁰⁴ “Regulations Amending Certain Regulations Concerning Drugs and Medical Devices (Shortages): SOR/2021-199,” Canada Gazette, Part II, Volume 155, Number 18 (01 September 2021), online: <<https://www.gazette.gc.ca/rp-pr/p2/2021/2021-09-01/html/sor-dors199-eng.html>>.

⁸⁰⁵ Executive Order 13944 of August 6, 2020, “Combating Public Health Emergencies and Strengthening National Security by Ensuring Essential Medicines, Medical Countermeasures, and Critical Inputs Are Made in the United States” (2020) 85:158 *Federal Register*.

⁸⁰⁶ US FDA, “Drug and Biologic Essential Medicines, Medical Countermeasures, and Critical Inputs for the List Described in Section 3(c) of the Executive Order 13944” (30 October 2020), online: <<https://www.fda.gov/media/143406/download>>.

Critical Inputs Are Made in the United States”. The definition of essential medicine differs from that of the WHO, with a focus on drugs (and other tools like diagnostics) needed to treat immediately life-threatening conditions in an acute care setting, to the explicit exclusion of drugs for longer-term use.⁸⁰⁷ However, this list demonstrates how the concept of Essential Medicines can be adapted to meet particular goals – in this case, the goal of maximizing domestic self-sufficiency (including not only specific drugs but APIs) in the event of a public health emergency. It also means that the United States, unlike Canada, has established an Essential Medicines List (albeit a narrowly defined one) as a tool to guide regulatory reforms to proactively ensure domestic access to certain drugs. More broadly, looking to solutions elsewhere offers Canada new opportunities for global collaboration – even if overcoming the nationalistic tendencies around drug supplies that have burgeoned during the pandemic may prove a challenge. However, even where direct cross-border collaboration does not occur, ideas may still transcend frontiers. Proactively listing Essential Medicines will hopefully be one such idea. Nonetheless, the response to drug shortages is not one that can be contained within Canada’s borders.

⁸⁰⁷ US FDA, “Criteria For Identifying Human Drug and Biologic Essential Medicines, Medical Countermeasures, and Critical Inputs for the List Described in Section 3(c) of the Executive Order (EO) 13944” (30 October 2020), online: <<https://www.fda.gov/media/143407/download>>.

Chapter 8: A new world for old drugs

Neglected Diseases: Not just someone else's problem

As discussed above, COVID-19 has drawn new attention to long-overlooked drugs for Neglected Diseases. At the same time, broader systemic issues, and their solutions, are still overshadowed by hot topics like the politicisation of ivermectin, just as a previous surge of attention due to off-patent trolling tended to focus on the scapegoating of Martin Shkreli. A longstanding barrier to tackling Neglected Diseases in high-income countries like Canada is that the diseases themselves are thought of as a problem of LMICs or a historical artifact, perceptions that can be woefully inaccurate. A recent commentary by Peter Sands, Executive Director of the Global Fund to Fight AIDS, Tuberculosis, and Malaria, raises the important question of why diseases like malaria and TB are no longer referred to as pandemics once they have been controlled in wealthier countries, but rather as epidemics or endemic diseases: “These distinctions have disturbing implications: By epidemic we actually mean a pandemic that no longer kills people in rich countries. By endemic we actually mean a disease the world could get rid of but hasn’t”.⁸⁰⁸ At the same time, framing TB, malaria and other Neglected Diseases as a problem that is today restricted to other – read: poorer and less developed – countries also enforces domestic barriers in high-income countries as well. It marginalizes both the diseases themselves, and the populations most at risk from them; this in turn serves to marginalize both developing new treatments, and ensuring access to existing ones. While thus far this thesis has concentrated on the implications for low-burden HICs, lack of attention to old Essential Medicines for Neglected Diseases poses global risks.

Like drug shortages, Neglected Diseases are a global problem. As the 2016 report by the UN Secretary-General’s High-Level Panel on Access to Medicines notes, “an estimated 1.7 billion people in 185 countries needed mass and/or

⁸⁰⁸ Sands, Peter, “Why aren’t diseases like HIV and malaria, which still kill millions of people a year, called pandemics?”, *STAT News* (6 July 2021), online: <https://www.statnews.com/2021/07/06/why-arent-diseases-like-hiv-and-malaria-which-still-kill-millions-of-people-a-year-called-pandemics/>.

individual treatment and care for neglected tropical diseases (NTDs)".⁸⁰⁹ This illustration of the global reach of "tropical" diseases offers a prime example of how even emphasizing the term "Neglected Tropical Disease" has the potential to be counterproductive, both narrowing the concept of Neglected Diseases and serving to situate these diseases as a problem restricted to a particular region rather than emphasizing the global nature of a problem that affects virtually every country in the world to some degree, and disproportionately affects the most vulnerable wherever they are located. Indeed, at worst reference to the tropics carries connotations of the tropical medicine of the colonial era, with salvation coming from wealthy countries themselves unafflicted with disease.

Neglected Diseases are also an area where international targets are set, and where HICs too may fall short. United Nations Sustainable Development Goal 3.3 is to "end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases" by 2030.⁸¹⁰ In 2018, Canada submitted its first Voluntary National Review of its Implementation of the 2030 Agenda for Sustainable Development.⁸¹¹ In this review, Canada only submitted incidence metrics for four diseases across all of these categories.⁸¹² This is despite the fact that numerous other diseases falling within the scope of Goal 3.3 are encountered in Canada; some of the omitted diseases are not only notifiable diseases in Canada, but were notified during this same period, meaning data was available.⁸¹³ Given Canada submitted metrics for malaria, endemicity of a disease cannot be the sole explanation. Notably, of this small selection of diseases for which data was actually submitted by Canada, only one had declined over the review period; incidence of the other three, including both

⁸⁰⁹ United Nations Secretary-General's High-Level Panel on Access to Medicines, *Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines*, by United Nations Secretary-General's High-Level Panel on Access to Medicines (2016).

⁸¹⁰ United Nations, *Transforming Our World: The 2030 Agenda for Sustainable Development*, by United Nations, A/RES/70/1 (New York: United Nations, 2015).

⁸¹¹ Global Affairs Canada, *Canada's implementation of the 2030 Agenda for Sustainable Development: voluntary national review* (2018).

⁸¹² Tuberculosis, malaria, hepatitis B and HIV

⁸¹³ For a list of other notifiable diseases, including Neglected Diseases like leprosy, see Public Health Agency of Canada, "Case definitions: Nationally notifiable diseases", online: <<https://diseases.canada.ca/notifiable/diseases-list>>.

malaria and tuberculosis, had all *increased*.⁸¹⁴ While the absolute numbers remain small, this highlights the need to take these conditions and other Neglected Diseases seriously.⁸¹⁵

There are a number of different ways of looking at the issue of once-important diseases becoming lower priorities as patterns of disease change. In 1971, Abdel Omran put forward his influential theory of the Epidemiologic Transition.⁸¹⁶ Per this model, societies undergo long-term shifts in mortality and disease patterns as they develop. In the initial stage, societies face famine and high levels of infectious disease; by the third and final stage, degenerative and non-communicable diseases such as cancer and heart disease are the chief form of morbidity and death. Today, while famine and infectious disease are still primary concerns in some countries, HICs like Canada have firmly transitioned to the third stage. The result is that the top public health priorities of countries at different stages are not the same, even though only one universal WHO MEML exists. This is clear when it comes to Neglected Diseases, whose impact is felt most strongly – though, it must be emphasized once again, not solely – in countries in the earlier stages of Omran’s model. This also means that many of the countries with the most resources to ensure access to Essential Medicines for infectious diseases (Neglected and otherwise) will have the lowest burden of them; paradoxically, this means such diseases are less likely to be prioritized even as they could in practice be more readily addressed.⁸¹⁷ This leads to important questions about the concept of Essential Medicines themselves.

⁸¹⁴ Global Affairs Canada, *Canada’s implementation of the 2030 Agenda for Sustainable Development: voluntary national review* (2018) at p.130. TB incidence per 100,000 increased from 4.6 to 4.8; malaria incidence per 100,000 (ignoring an obvious typo that lists it per 1000!) increased from 1.26 to 1.55.

⁸¹⁵ Particularly given the low numbers, these increases may not necessarily reflect major trends, and may have some other explanation; nonetheless, an increase in three out of four surely merits the provision of such explanations.

⁸¹⁶ Omran, Abdel R, “The epidemiologic transition: a theory of the epidemiology of population change. 1971” (2005) 83:4 *Milbank Q* 731–757.

⁸¹⁷ While beyond the scope of this thesis, these challenges go both ways, as conditions associated with the third stage, such as cancer and heart disease, become more prevalent outside HICs, creating a double burden of disease in settings with fewer resources to address them. See e.g., Bygbjerg, I C, “Double Burden of Noncommunicable and Infectious Diseases in Developing

For one, the possibility of any society attaining the third stage of the epidemiologic transition is itself a relatively recent achievement for humankind. Not all that long ago, infectious disease would have exacted a considerable toll in what are now high-income developed countries. For instance, at the time of Canadian Confederation in 1867, tuberculosis was the nascent country's leading cause of death.⁸¹⁸ Today, by contrast, tuberculosis is a disease consigned to the history books for most Canadians. This does not mean tuberculosis is no longer a problem in Canada today. It remains a very serious threat to many of Canada's politically and economically marginalized populations, particularly Indigenous communities in Canada's North; TB rates among Inuit are nearly 300 times higher than among non-Indigenous people born in Canada.⁸¹⁹ Migrant populations from less wealthy countries bear the brunt of drug-resistant TB.⁸²⁰ Together, Indigenous communities and people born outside of Canada account for close to 90% of all cases of TB in Canada.⁸²¹ Even more broadly, tuberculosis has been called the archetypal disease of poverty.⁸²² Underscoring the roles of poverty and intersectional marginalization, street-involved populations are another group at risk of TB in Canada.⁸²³ The disease also disproportionately affects other groups that are particularly dependent upon the state to meet their health needs, such as people in correctional facilities.⁸²⁴ By contrast, those with little to fear from TB –

Countries" (2012) 337:6101 *Science* 1499–1501, online:

<<https://www.science.org/doi/10.1126/science.1223466>>.

⁸¹⁸ Public Health Agency of Canada, "The Chief Public Health Officer's Report on the State of Public Health in Canada, 2013: Infectious Disease—The Never-ending Threat" (Public Health Agency of Canada, 2013), online: <<https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/cphorsphc-respcacsp/2013/assets/pdf/2013-eng.pdf>>, p.40.

⁸¹⁹ Tam, Theresa, *The Time Is Now: CPHO Spotlight on Eliminating Tuberculosis in Canada* (Public Health Agency of Canada, 2018) at p.2.

⁸²⁰ LaFreniere, Marie et al., "Tuberculosis drug resistance in Canada: 2018" (2020) 46:1 *Can Commun Dis Rep* 9–15.

⁸²¹ Tam, Theresa. *The Time Is Now: CPHO Spotlight on Eliminating Tuberculosis in Canada* Public Health Agency of Canada, 2018), p.8.

⁸²² The Lancet, "Tackling poverty in tuberculosis control" (2005) 366:9503 *The Lancet* 2063, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673605678622>>.

⁸²³ See e.g., Aho, J et al., "Outbreak of tuberculosis among substance users and homeless people in Greater Montréal, Canada, 2003-2016" (2017) 43:3–4 *Can Commun Dis Rep* 72–76.

⁸²⁴ The considerable body of literature on TB in correctional facilities is beyond the scope of this thesis, but see e.g., Kouyoumdjian, Fiona et al., "Health status of prisoners in Canada: Narrative review" (2016) 62:3 *Can Fam Physician* 215–222.

Canadian-born, non-Indigenous people not living in poverty – are also those most likely to hold financial and political capital. Thus, a disease that was once a major public health concern for all Canadians has slipped dramatically as a national priority (something also reflected in the fact that tuberculosis data in Canada is frequently years out of date).⁸²⁵ While Canadian officials may periodically assert, as Canada’s Chief Public Health Officer did in 2018, that “the time is now” to address tuberculosis, rhetoric has been more plentiful than action on issues ranging from tackling underlying social inequalities that fuel the disease to ensuring domestic access to Essential Medicines to treat it.⁸²⁶ This problem of perceiving Neglected Diseases as an issue of the long ago and the far away is not a new one. Consider this Canadian commentary from nearly fifty years ago: “The most reasonable definition of ‘tropical diseases’ therefore, is those conditions commonly occurring in warm climates. Today the poor peoples of the world live mainly in warm climates and it is here that diseases like tuberculosis and typhoid fever occur frequently”.⁸²⁷

If a disease has been declared a global emergency – as tuberculosis was, over a quarter century ago – can individual countries ignore international priorities in setting their domestic ones simply because the problem is more severe elsewhere?⁸²⁸ Can a high-income country de-prioritize a disease that is no longer common domestically, particularly if it lingers in vulnerable groups who may be the most in need of protection by the state? In turn, does an Essential Medicine to

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⁸²⁵ See e.g., Heffernan, Courtney, “Tuberculosis in Canada: who counts?” (2021) 112:3 Can J Public Health 541–542, online: <<https://link.springer.com/10.17269/s41997-021-00506-7>>.

⁸²⁶ Tam, Theresa. *The Time Is Now: CPHO Spotlight on Eliminating Tuberculosis in Canada*, by Theresa Tam (Public Health Agency of Canada, 2018).

⁸²⁷ Le Riche, W Harding & M M Lenczner, “New migration pattern increases incidence in Canada of diseases common in tropical areas” (1973) 109:6 Can Med Assoc J 546–548. Typhoid too had once been serious public health concern in Canada; like TB, it remains regularly reported here. For the history of typhoid in Canada, see e.g., Howard, Norman J, “The Progressive Fight against Typhoid Fever in Canada during the Past Twenty Years: With Special Reference to the Controlling Factors” (1932) 23:8 Canadian Public Health Journal 376–838; Skoll, S L & H O Dillenberg, “Typhoid fever: a Saskatchewan saga” (1962) 87 Can Med Assoc J 397–404.

⁸²⁸ WHO Global Tuberculosis Programme, *TB : a global emergency, WHO report on the TB epidemic*, by WHO Global Tuberculosis Programme, WHO/TB/94.177 (World Health Organization, 1994). This emergency has never been rescinded, something reasserted at the first UN General Assembly High-Level Meeting on the fight against tuberculosis in 2018: United Nations General Assembly, *Political Declaration of the UN General Assembly High-Level Meeting*, Resolution A/RES/73/3 (2018). See also “End the tuberculosis emergency: a promise is not enough” (2019) 394:10208 The Lancet 1482, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673619324596>>.

treat a less common disease become any less Essential to those individuals still affected by that disease? Such questions implicate the moral and legal differences between the situation where a drug is unavailable due to barriers such as resource constraints, and one where sufficient resources are available, but access is constrained by both private commercial interests and the very regulatory bodies intended to protect the health of citizens.

A changing world also affects patterns of disease in ways that go beyond Omran's progression. In some cases, wealthy countries may make considerable headway in tackling a disease, controlling or perhaps even eliminating it domestically; barring smallpox, however, no human disease has ever been totally eradicated in nature.⁸²⁹ Once-forgotten diseases have the potential return to old territories, or spread to new ones; others, like TB, continue to exert an overlooked burden. Some examples of this have already been discussed. The emergence, and re-emergence, of Neglected Disease in high-income states are not novel trends either, even if they have changed over time. As noted earlier, Neglected Diseases like leprosy, tuberculosis and trachoma have been drivers of Canadian immigration law and policy for over a century.⁸³⁰ Even in the post-World War II era of medical and public health successes against old foes in HICs, warnings of an increase in Neglected Diseases as a result of both travel and migration have been sounded in Canada since at least the 1960s.⁸³¹ They were reiterated in the 1970s as travel and migration patterns – and Canada's immigration laws – evolved.⁸³² Even the possibility of encountering "exotic" Neglected Diseases in medical practice in small

⁸²⁹ Dowdle, W R, "The principles of disease elimination and eradication" (1998) 76 Suppl 2 Bull World Health Organ 22–25. The "human" qualifier is in reference to rinderpest, a viral disease primarily associated with cattle. See e.g., Morens, David M et al., "Global rinderpest eradication: lessons learned and why humans should celebrate too" (2011) 204:4 J Infect Dis 502–505.

⁸³⁰ See e.g., Vineberg, Robert, "Healthy Enough to Get In: The Evolution of Canadian Immigration Policy Related to Immigrant Health" (2015) 16:2 Int Migration & Integration 279–297; Byers, W Gordon M, "Trachoma in Canada" (1932) 27:4 Can Med Assoc J 372–376.

⁸³¹ Lenczner, M & T Owen, "The impact of tropical and parasitic diseases in a non-endemic area" (1960) 82 Can Med Assoc J 805–812.

⁸³² White, F M, "Imported diseases: an assessment of trends" (1977) 117:3 Can Med Assoc J 241–245; le Riche, W Harding & M M Lenczner, "New migration pattern increases incidence in Canada of diseases common in tropical areas" (1973) 109:6 Can Med Assoc J 546–548.

urban centres in Canada rather than solely its major metropolises is nothing new.⁸³³

Nevertheless, travel and migration have continued to expand, while new issues such as climate change have also entered the discussion in recent years, not merely in Canada but at the global level.⁸³⁴ For instance, reflecting upon repeated incidents of dengue transmission in Europe, and the presence of numerous other Neglected Diseases – like Chagas disease, cysticercosis, echinococcosis, toxocariasis, and West Nile virus – in the United States, a 2014 editorial in *The Lancet Infectious Diseases* bore the rather telling title “Neglected tropical diseases: no longer someone else’s problem”.⁸³⁵ By 2018, a study concluded that leishmaniasis had not only become endemic in the United States, but was acquired endemically more frequently than via international travel.⁸³⁶ Other models have suggested leishmaniasis could extend its range as far as southern Canada in coming decades, a northward expansion facilitated by climate change.⁸³⁷ Similarly, in a 2018 letter to *The Lancet*, the former Director of the WHO Department of Control of Neglected Tropical Diseases emphasized the need for WHO leadership, noting, among other things, the importance of “controlling the emergence and re-emergence of some NTDs, such as hookworm in the south of the USA or urogenital schistosomiasis in Corsica”.⁸³⁸

Even before accounting for travel and climate change, another factor to consider when it comes to domestic neglect of Neglected Diseases is that some of what is viewed as re-emergence may actually have been there all along. Peter Hotez

⁸³³ Chatterton, R T, “Exotic diseases are common” (1977) 23 Can Fam Physician 73–78.

⁸³⁴ Acknowledging, of course, the recent impacts of COVID-19 on travel and migration patterns, though it remains unclear what this impact may be in the longer term. Climate change remains a pressing concern either way.

⁸³⁵ The Lancet Infectious Diseases. “Neglected tropical diseases: no longer someone else’s problem” (2014) 14:10 The Lancet Infectious Diseases 899, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1473309914709284>>.

⁸³⁶ McIlwee, Bridget E, Stephen E Weis & Gregory A Hosler, “Incidence of Endemic Human Cutaneous Leishmaniasis in the United States” (2018) 154:9 JAMA Dermatol 1032, online: <<http://archderm.jamanetwork.com/article.aspx?doi=10.1001/jamadermatol.2018.2133>>.

⁸³⁷ González, Camila et al., “Climate Change and Risk of Leishmaniasis in North America: Predictions from Ecological Niche Models of Vector and Reservoir Species” (2010) 4:1 PLoS Negl Trop Dis e585, online: <<https://dx.plos.org/10.1371/journal.pntd.0000585>>.

⁸³⁸ Savioli, Lorenzo & Denis Daumerie. “WHO leadership is essential for the elimination of NTDs” (2018) 390:10114 Lancet 2765.

– one of the originators of the Neglected Tropical Disease (NTD) concept – has been at the forefront of examining the issue of Neglected Diseases in high-income countries, including via his concept of “Blue Marble Health”.⁸³⁹ Blue Marble Health refers to “new and somewhat paradoxical findings” that poor people living in high and middle-income countries account for a majority of the world’s disease burden for many Neglected Diseases.⁸⁴⁰ This includes “millions of Americans living in the United States with an NTD and a significant but mostly hidden level of poverty and disease in Europe and Australia”.⁸⁴¹ His findings apply to Canada too; his volume dedicated to Blue Marble Health draws particular attention to Indigenous populations in northern Canada. Here, Hotez highlights that NTD infections are regular occurrences in this decidedly non-tropical region, including echinococcosis, trichinellosis and toxoplasmosis.⁸⁴² Furthermore, additional diseases could pose risks in the region in future:

A circumpolar working group has convened and identified a group of parasitic and zoonotic infections as likely candidates to increase in prevalence as a consequence of climate change, including those highlighted above, in addition to some bacterial NTDs such as anthrax, leptospirosis, and tularemia and viral NTDs including West

⁸³⁹ Arguably the seminal paper in drawing attention to NTDs as a collective concept is Molyneux, David H, Peter J Hotez & Alan Fenwick, “‘Rapid-impact interventions’: how a policy of integrated control for Africa’s neglected tropical diseases could benefit the poor” (2005) 2:11 PLoS Med e336, which proposed a list of 13 diseases and interventions involving drugs like ivermectin and albendazole. Molyneux himself would later describe NTDs as a “brand identity”. Molyneux, David H, “The ‘Neglected Tropical Diseases’: now a brand identity; responsibilities, context and promise” (2012) 5:1 Parasites Vectors 23, 1756-3305-5-23, online: <<https://parasitesandvectors.biomedcentral.com/articles/10.1186/1756-3305-5-23>>.

⁸⁴⁰ Hotez, Peter J. “Ten failings in global neglected tropical diseases control” (2017) 11:12 PLoS Negl Trop Dis e0005896, online: <<https://dx.plos.org/10.1371/journal.pntd.0005896>>.

⁸⁴¹ Hotez, Peter J. “Ten failings in global neglected tropical diseases control” (2017) 11:12 PLoS Negl Trop Dis e0005896, online: <<https://dx.plos.org/10.1371/journal.pntd.0005896>>.

⁸⁴² Hotez, Peter J. *Blue marble health: an innovative plan to fight diseases of the poor amid wealth* (Baltimore: Johns Hopkins University Press, 2016) p.115.

Nile virus infection, tick-borne encephalitis, and hantavirus infection.⁸⁴³

Hotez himself views the purpose of Blue Marble Health as an advocacy tool to encourage greater action by the G20 around these diseases: Blue Marble Health “has the potential to be shaped into a new policy framework as it suggests that a substantial portion of the world’s NTDs, up to one-half, or more, in some cases, may be eliminated if each of the G20 countries would assume greater responsibility for their own NTD problem and expand their indigenous control and elimination efforts”.⁸⁴⁴ Whether or not his particular model and terminology are adopted, the problem Hotez outlines should not be ignored. Canada, like its G20 fellows, has a role to play in this regard, both at home and abroad.

After all, there was a time when at least some of these diseases used to attract considerable government attention in today’s HICs. Indeed, addressing these diseases may have helped HICs to advance to their current stage of development. One study suggests that historical hookworm eradication programs in the American South in the early 20th Century yielded substantial social and economic benefits, going so far as to offer estimates that “the hookworm infection rate could account for around half of the literacy gap and about 20 percent of income differences, and so eradication would have closed [the gap between Northern and Southern US States] by a similar amount.”⁸⁴⁵ Regardless of the precise accuracy of this calculation, it illustrates the broader point that taking a Neglected Disease seriously can pay dividends. Similar economic dividends have

⁸⁴³ Hotez uses an expansive definition of NTD here; given his role in creating the term, this seems his prerogative. Hotez, Peter J. *Blue marble health: an innovative plan to fight diseases of the poor amid wealth* (Baltimore: Johns Hopkins University Press, 2016) p.115.

⁸⁴⁴ Hotez, Peter J. “NTDs V.2.0: ‘blue marble health’--neglected tropical disease control and elimination in a shifting health policy landscape” (2013) 7:11 PLoS Negl Trop Dis e2570.

⁸⁴⁵ Bleakley, H. “Disease and Development: Evidence from Hookworm Eradication in the American South” (2007) 122:1 The Quarterly Journal of Economics 73–117, online: <<https://academic.oup.com/qje/article-lookup/doi/10.1162/qjec.121.1.73>>. However, the precise benefits that can be directly attributed to deworming programs have been questioned, see e.g., Miguel, Edward & Michael Kremer, “Worms: Identifying Impacts on Education and Health in the Presence of Treatment Externalities” (2004) 72:1 Econometrica 159–217, online: <<http://doi.wiley.com/10.1111/j.1468-0262.2004.00481.x>>.

been claimed for countries that eradicated malaria decades ago, such as those in Southern Europe.⁸⁴⁶

At the same time, such successes also perpetuate a conundrum for Neglected Diseases, both locally and globally. Diseases that are out of sight may easily pass out of mind. For many Neglected Diseases, “goals for elimination as a public health problem explicitly allow for elimination to be certified despite low levels of disease transmission”.⁸⁴⁷ The risk, as Sun and Amon highlight, is that this will “concentrate the remaining disease burden in the most vulnerable while simultaneously ending funding and outreach”.⁸⁴⁸ Vulnerable populations in the Global North can attest to this fact, with a lack of access to Essential Medicines, be they antiparasitics or for TB treatment, serving to both exemplify and exacerbate the problem. As Hotez concludes of the G20 nations: “The bottom line is that each of these nations has the internal capacity to provide these low-cost treatments to its impoverished populations”.⁸⁴⁹ However, in these same countries, including Canada, that capacity is not always used. Explicitly identifying overlooked public health problems – including the Essential Medicines to treat them – is an important step; here, the WHO MEML provides a universal reference point. As such, it also serves as a point of reference for vital tools whose absence is not recognized until they are needed once again.

Diphtheria: The strangling of supply

The dangers of neglecting a disease can manifest not merely at the national level but the global one; they can include the risk of a landmark Essential Medicine necessary to treat a once widespread and still deadly scourge vanishing before the

⁸⁴⁶ Gallup, JL & JD Sachs, “The economic burden of malaria” (2001) 64:1_suppl The American Journal of Tropical Medicine and Hygiene 85–96, online: <<https://ajtmh.org/doi/10.4269/ajtmh.2001.64.85>>. While influential, however, these findings have not gone unquestioned. See e.g., Sarma, Nayantara et al., “The Economic Burden of Malaria: Revisiting the Evidence” (2019) 101:6 The American Journal of Tropical Medicine and Hygiene 1405–1415, online: <<https://ajtmh.org/doi/10.4269/ajtmh.19-0386>>.

⁸⁴⁷ Sun, Nina & Joseph J Amon. “Addressing Inequity: Neglected Tropical Diseases and Human Rights” (2018) 20:1 Health Hum Rights 11–25.

⁸⁴⁸ Sun, Nina & Joseph J Amon. “Addressing Inequity: Neglected Tropical Diseases and Human Rights” (2018) 20:1 Health Hum Rights 11–25.

⁸⁴⁹ Hotez, Peter J. *Blue marble health: an innovative plan to fight diseases of the poor amid wealth* (Baltimore: Johns Hopkins University Press, 2016) p.144.

disease itself does.⁸⁵⁰ This public health failure can be an unfortunate side-effect of other public health successes. Consider diphtheria. Caused by the bacterium *Corynebacterium diphtheriae*, this disease derives its name from a particularly unpleasant characteristic of the respiratory form of the disease.⁸⁵¹ Typically affecting the nose and throat, the bacteria secrete a toxin that in turn causes a thick grey membrane of dead cells and bacteria to form, blocking the patient's airways. In 1826, a French physician christened the disease after this membrane, from the Greek "diphthera", meaning leather or hide.⁸⁵² Colloquial names, like "the strangling angel" were no more charming.⁸⁵³ All were fitting monikers, however, for a major public health threat. In the early 1920s, for instance, it was the most common cause of death in Canadian children 2-14, counting for roughly one in every seven deaths.⁸⁵⁴

Under such circumstances, the development of the first effective treatment, diphtheria antitoxin (DAT), in the late 19th Century was a landmark moment in medical science. Diphtheria was the first bacterial disease ever to be successfully treated with an antitoxin.⁸⁵⁵ Its development was a high profile event, with teams of French and German researchers competing for national honour.⁸⁵⁶ In 1901, the very first Nobel Prize in Physiology or Medicine was awarded to Emil von Behring, "for his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and

⁸⁵⁰ Adler, N R, A Mahony & N D Friedman, "Diphtheria: forgotten, but not gone" (2013) 43:2 Intern Med J 206–210.

⁸⁵¹ Note: The author acknowledges other species of *Corynebacterium* like *C. ulcerans* may also be implicated, but will not go into that level of microscopic detail, as it were.

⁸⁵² "Etymologia: Diphtheria" (2013) 19:11 Emerg Infect Dis, online: <http://wwwnc.cdc.gov/eid/article/19/11/ET-1911_article.htm>.

⁸⁵³ Byard, Roger W, "Diphtheria - 'The strangling angel' of children" (2013) 20:2 J Forensic Leg Med 65–68.

⁸⁵⁴ Fitzgerald, J G et al. "Experiences with Diphtheria Toxoid in Canada" (1932) 22:1 Am J Public Health Nations Health 25–28, online: <<http://ajph.aphapublications.org/doi/10.2105/AJPH.22.1.25>>.

⁸⁵⁵ Kleinman, L C, "To end an epidemic. Lessons from the history of diphtheria" (1992) 326:11 N Engl J Med 773–777.

⁸⁵⁶ Huentelmann, Axel C. "Two Cultures of Regulation? The Production and State Control of Diphtheria Serum at the End of the Nineteenth Century in France and Germany" (2007) 6:2 Hygiea 99–120, online: <http://www.ep.liu.se/ej/hygiea/hygiea_article.asp?doi=10.3384/hygiea.1403-8668.077199>.

deaths”.⁸⁵⁷ It would similarly help cement the status of the Pasteur Institute in France; building upon the renown of Louis Pasteur’s rabies vaccine (also a scientific and medical breakthrough, but used to treat relatively few people by comparison), “the treatment of diphtheria would come to occupy a crucial position in the prolongation of the Pasteur myth —now centered on the institute that bore his name— being the first major disease to be successfully treated by a microbiological technique”.⁸⁵⁸ It has been argued that in the United States, the successful use of DAT (and public awareness of that success) played a major role in establishing medicine as a scientific profession.⁸⁵⁹ These developments and their benefits were monitored in Canada as well; for instance in 1910, a number of prominent physicians approached the Ontario Cabinet asking that a Pasteur Institute be established in Toronto.⁸⁶⁰

In turn, DAT itself played a crucial role in Canada’s history of access to medicines. The COVID-19 pandemic has reignited interest in this period, resulting in the op-ed pages being rife with nostalgic commentary on the historical precedent of Connaught Laboratories (“Connaught Labs”), a non-commercial facility that played an important role not only in many important medical discoveries, but also in ensuring affordable access to them.⁸⁶¹ The most famous of

⁸⁵⁷ “The Nobel Prize in Physiology or Medicine 1901”. NobelPrize.org. Nobel Media AB 2020. Online: <<https://www.nobelprize.org/prizes/medicine/1901/summary/>>.

⁸⁵⁸ Simon, Jonathan. “The origin of the production of diphtheria antitoxin in France, between philanthropy and commerce” (2007) 27 *Dynamis* 63–82.

⁸⁵⁹ Kleinman, L C, “To end an epidemic. Lessons from the history of diphtheria” (1992) 326:11 *N Engl J Med* 773–777.

⁸⁶⁰ “A Pasteur Institute” (1910) 43:7 *The Canada Lancet* 554, online: <https://www.canadiana.ca/view/oocihm.8_05199_475/74?r=0&s=1>.

⁸⁶¹ See e.g., (though there are more) McQuaig, Linda, “When Canada was a world leader in vaccine research and production”, *The Toronto Star* (30 November 2020), online: <<https://www.thestar.com/opinion/contributors/2020/11/30/when-canada-was-a-world-leader-in-vaccine-research-and-production.html>>; “Editorial: Vaccine production belongs in public hands”, *The Times Colonist* (27 February 2021), online: <<https://www.timescolonist.com/opinion/editorials/editorial-vaccine-production-belongs-in-public-hands-1.24287859>>; Olive, David, “Canada needs the Connaught model of domestic vaccine production”, *The Toronto Star* (20 March 2021), online: <<https://www.thestar.com/business/opinion/2021/03/20/canada-needs-the-connaught-model-of-domestic-vaccine-production.html>>; Thomas, William, “Connaught Labs — the greatest mistake ever made by a Canadian government”, *St Catharines Standard* (22 February 2021), online: <<https://www.stcatharinesstandard.ca/local-niagara->

these is insulin, developed at Connaught Labs a century ago, and still the default answer to trivia questions on the most important Canadian contribution to medical innovation.⁸⁶² Connaught would also play an important role in vital public health campaigns against diseases such as polio and smallpox, both at home and abroad, exporting vaccines and antitoxins throughout the British Empire and beyond.⁸⁶³ Initially affiliated with the University of Toronto, then owned by a public/private venture called the Canada Development Corporation, the ultimate privatization of Connaught Labs and its sale to a foreign pharmaceutical company have been evoked as an example of a wrong that Canada should right in the wake of COVID-19 by restoring a central role for public ownership and domestic production in the pharmaceutical industry.⁸⁶⁴ Often overlooked in this story, however, is that diphtheria antitoxin was in fact Connaught Labs' *raison d'être*. In turn, DAT offers a prime example of the sort of product that could benefit from production removed from commercial considerations for both national and international distribution.

As far back as 1895, an editorial in *The Canada Lancet* was cautious about the newly invented antitoxin, but suggested: "If the anti-toxine <sic> can be shown to be of any great value [...] especially in laryngeal cases, and will prevent the death of any considerable per cent of them, then, and then only, will it be accepted as a valuable addition to our armamentarium of cures for diphtheria".⁸⁶⁵ It also raised questions about who might manufacture such a product; concerned about both fraud and speculation, it reached the following conclusion: "To our mind there is but one way to be certain that we are procuring anti-toxine in the blood serum that we may demand; that is that the Government take hold of this matter and employ

[falls/opinion/columnists/2021/02/22/connaught-labs-the-greatest-mistake-ever-made-by-a-canadian-government.html](https://www.canadiana.ca/view/oocihm.8_05199_294/26?r=0&s=1)>.

⁸⁶² Rutty, Christopher J, "'Couldn't live without it': diabetes, the costs of innovation and the price of insulin in Canada, 1922-1984" (2008) 25:2 Can Bull Med Hist 407-431.

⁸⁶³ See e.g., Rutty, Christopher J, "Canadian Vaccine Research, Production and International Regulation: Connaught Laboratories and Smallpox Vaccines, 1962-1980," in Kenton Kroger, Jennifer Keelan and Pauline M.H. Mazumdar (eds.) *Crafting Immunity: Working Histories of Clinical Immunology* (Ashgate, April 2008), p.273-300.

⁸⁶⁴ This is a common theme in the op-eds cited earlier. The standard potted history of Connaught Labs oversimplifies the situation somewhat, and will be revisited.

⁸⁶⁵ "Treatment of Diphtheria with Anti-toxine" (1895) 27:6 *The Canada Lancet* 189-90, online: <https://www.canadiana.ca/view/oocihm.8_05199_294/26?r=0&s=1>.

salaried officials to carefully prepare and preserve the serum for use as it may be demanded".⁸⁶⁶

DAT did become available in Canada shortly thereafter, but only as an expensive import. A further *Canada Lancet* editorial in 1905 noted a death rate from diphtheria in Ontario as high as 12 percent, something "we fear is due to the expense of the antitoxin placing it beyond the reach of some of the poorer patients".⁸⁶⁷ Thus, as Defries describes it, in the years before Connaught Labs, diphtheria in Canada:

[...] was a dread disease; during the five-year period 1911-1915 the average number of cases was 2,500 and the number of deaths 400. But diphtheria deaths could be prevented if the patient received serum (diphtheria antitoxin) promptly and in large amounts. This fact was well known, but the serum was not made in Canada and was very expensive.⁸⁶⁸

This gap between necessity and access led University of Toronto professor Dr. John G. Fitzgerald to begin production of DAT in Canada, with the goal of producing it at a low enough price that the government could provide it to patients for free.⁸⁶⁹ He began just before World War I. Within a few years, the laboratory had been christened in honour of the Duke of Connaught, then Governor-General of Canada. Other early projects included Canada's first domestically produced rabies vaccine (previously sourced, like DAT, from the US) and tetanus antitoxin during the war.⁸⁷⁰

⁸⁶⁶ "Treatment of Diphtheria with Anti-toxine" (1895) 27:6 *The Canada Lancet* 189-90, online: <https://www.canadiana.ca/view/oocihm.8_05199_294/26?r=0&s=1>.

⁸⁶⁷ "The Value of Diphtheria Antitoxin" (1905) 38:9 *The Canada Lancet* 836-837, online: <https://www.canadiana.ca/view/oocihm.8_05199_417/68?r=0&s=1>.

⁸⁶⁸ Defries, R D. "The Connaught Medical Research Laboratories, 1914-1948" (1948) 39:8 *Can J Public Health* 330-344.

⁸⁶⁹ Defries, R D. "The Connaught Medical Research Laboratories, 1914-1948" (1948) 39:8 *Can J Public Health* 330-344.

⁸⁷⁰ Ruttly, Christopher J, "Personality, Politics and Public Health: The Origins of Connaught Medical Research Laboratories, 1888-1917," in E.A. Heaman, Alison Li, Shelley McKellar (eds.) *Figuring the Social: Essays in Honour of Michael Bliss* (Toronto: University of Toronto Press, 2008), p. 273-303.

Once a diphtheria vaccine was developed in the 1920s, Connaught Labs started producing that as well.⁸⁷¹ In turn, the influence exerted by Fitzgerald and Connaught Labs would extend beyond Canada. By one British account, “As far as the rest of the English-speaking world was concerned the most influential person in actuating public health officials to immunize against diphtheria... was probably the Canadian, John Fitzgerald”.⁸⁷² The expansion of diphtheria vaccination decreased, but did not eliminate, the need for DAT. In Canada, the disease lingered for some decades yet. An account of a 1940-41 outbreak in Halifax, for instance, describes just under 900 cases and 22 deaths; diphtheria antitoxin figured heavily in the response.⁸⁷³ DAT similarly remained a valuable tool throughout the world, even as childhood vaccinations expanded. It appeared on the inaugural WHO MEML in 1977 and has remained there ever since.

Diphtheria vaccine has similarly been on the WHO MEML in some form (alone, or as a combination such as diphtheria-pertussis-tetanus vaccine, aka DPT) since 1977.⁸⁷⁴ Fast forward to the 21st Century, and the number of global cases of diphtheria has decreased dramatically, another success of universal childhood vaccination programmes. Today, the global burden of diphtheria has tumbled from around 100,000 cases annually in 1980; however, it has stalled at between 4000-6000 cases, with occasional spikes, for most of the 21st Century.⁸⁷⁵ While greatly diminished, it is not gone; in Canada, an imported case has caused the death of a patient as recently as 2020.⁸⁷⁶ As a result of the decline in cases, however, global demand for DAT has decreased dramatically; accordingly, so too has the number of

⁸⁷¹ Somewhat confusingly for the casual reader, “diphtheria toxoid” refers to the vaccine; it is not to be confused with diphtheria antitoxin (DAT). Moloney, P J. “The Preparation and Testing of Diphtheria Toxoid (Anatoxine-Ramon)” (1926) 16:12 *Am J Public Health* 1208–1210, online: <<http://ajph.aphapublications.org/doi/10.2105/AJPH.16.12.1208>>.

⁸⁷² Mortimer, P P, “The diphtheria vaccine debacle of 1940 that ushered in comprehensive childhood immunization in the United Kingdom” (2011) 139:4 *Epidemiol Infect* 487–493.

⁸⁷³ Morton, A R. “The Diphtheria Epidemic in Halifax” (1941) 45:2 *Canadian Medical Association Journal* 171–174.

⁸⁷⁴ The DPT vaccine itself was removed from the WHO MEML in 1999 as part of a shift away from including specific combination vaccines rather than the individual vaccines.

⁸⁷⁵ Clarke, Kristie E N et al., “Global Epidemiology of Diphtheria, 2000–2017” (2019) 25:10 *Emerg Infect Dis* 1834–1842.

⁸⁷⁶ Cholewa, Scott et al., “Fatal respiratory diphtheria in a visitor to Canada” (2021) 193:1 *CMAJ* E19–E22, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.200707>>.

producers of DAT. According to Health Canada’s Drug Product Database, the last approved DAT product left the Canadian market in 2000. Most of the world finds itself in a similar situation. Nonetheless, when cases of diphtheria occur, as thousands do around the world each year, DAT remains essential. A recent systematic review estimates that its administration decreases mortality by 76%.⁸⁷⁷ However, its effectiveness depends upon prompt administration, underscoring the need for ready access.⁸⁷⁸

Unfortunately, when old diseases re-emerge in places that have long forgotten them, the tools to treat them are not always still at hand. In the case of diphtheria, “it was the very successes with diphtheria prevention that had eroded the market for DAT in Europe and North America—and with it, the availability of treatment”.⁸⁷⁹ The practical impact of this situation briefly drew attention in 2015 and 2016, when poor access to DAT led to fatal cases of diphtheria in Spain and Belgium.⁸⁸⁰ In a rapid risk assessment of the Spanish case, the European Centre for Disease Prevention and Control stated that the “most urgent critical issue is the shortage of diphtheria antitoxin (DAT) for immediate use when clinicians suspect diphtheria”.⁸⁸¹ DAT was not available in either Spain or Belgium, nor in most of their neighbours; concerns had previously been raised about sourcing DAT from a dwindling number of suppliers, but insufficient measures had been taken to actually address those concerns.⁸⁸²

⁸⁷⁷ Truelove, Shaun A et al., “Clinical and Epidemiological Aspects of Diphtheria: A Systematic Review and Pooled Analysis” (2020) 71:1 Clin Infect Dis 89–97.

⁸⁷⁸ Truelove, Shaun A et al., “Clinical and Epidemiological Aspects of Diphtheria: A Systematic Review and Pooled Analysis” (2020) 71:1 Clin Infect Dis 89–97.

⁸⁷⁹ Vargha, Dora & Jeremy A Greene. “Grey-market medicines: diphtheria antitoxin and the decay of biomedical infrastructure” (2017) 389:10080 The Lancet 1690–1691, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673617310693>>.

⁸⁸⁰ Vargha, Dora & Jeremy A Greene. “Grey-market medicines: diphtheria antitoxin and the decay of biomedical infrastructure” (2017) 389:10080 The Lancet 1690–1691, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673617310693>>.

⁸⁸¹ European Centre for Disease Prevention and Control, “A case of diphtheria in Spain, 15 June 2015”, (2015), online: <<https://www.ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/diphtheria-spain-rapid-risk-assessment-june-2015.pdf>>.

⁸⁸² Both, L et al., “Access to diphtheria antitoxin for therapy and diagnostics” (2014) 19:24 Eurosurveillance, online: <<http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20830>>.

When this disease oft thought relegated to the past strikes, access to this Essential Medicine that is now well over a century old remains crucial to the response.⁸⁸³ In Europe, poor access had become the status quo even though the continent had received a blunt warning of the potential consequences of a resurgence of diphtheria, and of the risks of interrupting DAT supply, not so many years before. In the early 1990s, a large outbreak in multiple countries of the former Soviet Union following its collapse resulted in close to 5000 deaths and well over 150,000 cases, offering a stark illustration of the consequences of disrupting state health services like childhood vaccination.⁸⁸⁴ It also offered a microcosm of lessons, sadly not heeded, on ensuring stable access to Essential Medicines.

Prior to the dissolution of the USSR, all supplies of diphtheria vaccine and DAT came from the Russian SSR (i.e., Russia); newly independent states no longer had access to this supply, nor in most cases the financial resources either to begin domestic production or to acquire vaccines and DAT on the international market.⁸⁸⁵ The resulting case fatality rate – outside Russia, which had retained its

⁸⁸³ It should be noted that access to DAT itself is not the only casualty of diphtheria's disappearance. As doctors become less familiar with diphtheria in practice, diagnosis can be delayed. Delays in diagnosis further compromise the necessary arrangements – which are often increasingly complicated given supply issues – to acquire DAT in a timely manner. Wagner, KS et al. "A review of the international issues surrounding the availability and demand for diphtheria antitoxin for therapeutic use" (2009) 28:1 Vaccine 14–20, online:

<<https://linkinghub.elsevier.com/retrieve/pii/S0264410X09014418>>. Indeed, delays in diagnosis compounded the issue in the Spanish and Belgian cases. Vargha, Dora & Jeremy A Greene. "Grey-market medicines: diphtheria antitoxin and the decay of biomedical infrastructure" (2017) 389:10080 The Lancet 1690–1691, online:

<<https://linkinghub.elsevier.com/retrieve/pii/S0140673617310693>>. Delays in diagnosis have also been seen in Canada, as in the 2020 instance when a fatal case in a visitor from India was only diagnosed post-mortem. Cholewa, Scott et al., "Fatal respiratory diphtheria in a visitor to Canada" (2021) 193:1 CMAJ E19–E22, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.200707>>. This illustrates the observation that in recent years, due "to the rarity of cases in Western communities and atypical presentations, the diagnosis may only be established at autopsy". Byard, Roger W, "Diphtheria - 'The strangling angel' of children" (2013) 20:2 J Forensic Leg Med 65–68.

⁸⁸⁴ Galazka, A, "Implications of the diphtheria epidemic in the Former Soviet Union for immunization programs" (2000) 181 Suppl 1 J Infect Dis S244–248; Vitek, Charles. "Diphtheria in the Former Soviet Union: Reemergence of a Pandemic Disease" (1998) 4:4 Emerg Infect Dis 539–550, online: <<http://www.cdc.gov/ncidod/eid/vol4no4/vitek.htm>>.

⁸⁸⁵ Wagner, KS et al. "A review of the international issues surrounding the availability and demand for diphtheria antitoxin for therapeutic use" (2009) 28:1 Vaccine 14–20, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0264410X09014418>>.

production of and access to DAT – was high.⁸⁸⁶ While other parts of Europe did draw upon the post-Soviet outbreak to learn lessons on issues like surveillance, ensuring sustained access to DAT was not similarly prioritized.⁸⁸⁷ In Europe, immediately before the Spanish and Belgian cases, it was “the responsibility of each individual country to supply treatment for diphtheria in the event of a case, which... may necessitate negotiations with neighbouring countries if the case occurs in a country that does not hold DAT stocks”.⁸⁸⁸ While some European countries held stockpiles of DAT, others did not, or had allowed their stockpiles to expire. After the high profile deaths in Belgium and Spain, a 2017 report examining 30 EU and EEA member states found that only 14/30 reported that they had a DAT stockpile; one country (Belgium) explicitly noted it relied upon other countries having DAT.⁸⁸⁹ Of those 14 countries with stockpiles, at least 6 had procured their existing stockpile from a source that was no longer producing DAT.⁸⁹⁰ Two countries also remarked in the report that the European “migrant crisis” then underway might affect the need for DAT; one of these, Greece, lacked a stockpile, and requested a supply sufficient for 5-10 cases in response to concerns about migration.⁸⁹¹ The report concluded, “DAT availability and procurement systems need to be defined in the EU/EEA Member States. This is particularly important given the increasing

⁸⁸⁶ Wagner, KS et al. “A review of the international issues surrounding the availability and demand for diphtheria antitoxin for therapeutic use” (2009) 28:1 Vaccine 14–20, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0264410X09014418>>.

⁸⁸⁷ Vargha, Dora & Jeremy A Greene. “Grey-market medicines: diphtheria antitoxin and the decay of biomedical infrastructure” (2017) 389:10080 The Lancet 1690–1691, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673617310693>>.

⁸⁸⁸ Wagner, KS et al. “A review of the international issues surrounding the availability and demand for diphtheria antitoxin for therapeutic use” (2009) 28:1 Vaccine 14–20, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0264410X09014418>>.

⁸⁸⁹ European Centre for Disease Prevention and Control, *Gap analysis on securing diphtheria diagnostic capacity and diphtheria antitoxin availability in the EU/EEA*. (LU: Publications Office, 2017), online: <<https://www.ecdc.europa.eu/en/publications-data/gap-analysis-securing-diphtheria-diagnostic-capacity-and-diphtheria-antitoxin>> p.17-18.

⁸⁹⁰ European Centre for Disease Prevention and Control, *Gap analysis on securing diphtheria diagnostic capacity and diphtheria antitoxin availability in the EU/EEA*. (LU: Publications Office, 2017), online: <<https://www.ecdc.europa.eu/en/publications-data/gap-analysis-securing-diphtheria-diagnostic-capacity-and-diphtheria-antitoxin>> p.22.

⁸⁹¹ European Centre for Disease Prevention and Control, *Gap analysis on securing diphtheria diagnostic capacity and diphtheria antitoxin availability in the EU/EEA*. (LU: Publications Office, 2017), online: <<https://www.ecdc.europa.eu/en/publications-data/gap-analysis-securing-diphtheria-diagnostic-capacity-and-diphtheria-antitoxin>> p.18.

number of toxigenic isolates and population movements into Europe”.⁸⁹² To this day, however, actions to mitigate these concerns, such as regional stockpiling of supplies from a sustainable and reliable source, or indeed renewed production to serve the EU and EEA, have not yet been effectively implemented.

Even in the United States, the world’s largest market for pharmaceuticals, the last licenced product exited the market in 1996, and no manufacturer has tried to obtain US licensure for DAT since (as such, Canada actually maintained formal domestic market presence after the US).⁸⁹³ The departure of the last marketed product led the US CDC to procure a stockpile of the century-old drug from an unapproved source for distribution through the CDC Drug Service Formulary (discussed earlier) as an experimental drug.⁸⁹⁴ On this matter, Vargha and Greene echo an observation made at multiple junctures throughout this thesis in relation to off-patent Essential Medicines: That it is “worth pausing to consider the historical contortions necessary to reframe DAT as an ‘investigational new drug’ in the 21st century”.⁸⁹⁵

In turn, the stockpiling of DAT shows how tenuous reliance on foreign sources can be. The American supply of unapproved DAT was first obtained from the French producer Pasteur Mérieux until it too stopped production in 2002, at which point the source became the Instituto Butantan in Brazil.⁸⁹⁶ Currently, the most recent batch of DAT in the CDC’s stockpile has an expiry date of October 2010; in March 2020, testing on this batch and another that expired in 2007 showed they still met their labelled specifications, thus permitting their continued use and

⁸⁹² European Centre for Disease Prevention and Control, *Gap analysis on securing diphtheria diagnostic capacity and diphtheria antitoxin availability in the EU/EEA*. (LU: Publications Office, 2017), online: <<https://www.ecdc.europa.eu/en/publications-data/gap-analysis-securing-diphtheria-diagnostic-capacity-and-diphtheria-antitoxin>> p.23.

⁸⁹³ US CDC, “Notice to Readers: Availability of Diphtheria Antitoxin Through an Investigational New Drug Protocol” (2004) 53:19 MMWR Weekly 413, online: <<https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5319a3.htm>>.

⁸⁹⁴ This mechanism for access to unmarketed drugs in the US is discussed in more detail elsewhere in this thesis.

⁸⁹⁵ Vargha, Dora & Jeremy A Greene. “Grey-market medicines: diphtheria antitoxin and the decay of biomedical infrastructure” (2017) 389:10080 *The Lancet* 1690–1691, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673617310693>>.

⁸⁹⁶ “Notice to Readers: Availability of Diphtheria Antitoxin Through an Investigational New Drug Protocol” (2004) 53:19 MMWR Weekly 413, online: <<https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5319a3.htm>>.

punting the question of obtaining new supplies down the road.⁸⁹⁷ Such an approach seems a far cry from the era when a 1925 diphtheria outbreak in the northern Alaska town of Nome led to a famed effort to bring in DAT by dog sled, which became a national *cause célèbre* (and one that would inspire Hollywood movies for decades to come, including, somewhat inexplicably at a time when diphtheria and DAT have faded from memory, two competing feature films in 2019).⁸⁹⁸

Back in Canada, in the post-Connaught Labs era, DAT has been imported from unapproved sources through the SAP and held in domestic stockpiles at the provincial level.⁸⁹⁹ Detailed information on the age and source of these stockpiles has been difficult to obtain; however, material from Alberta suggests that DAT was obtained from the Instituto Butantan in Brazil from 2006-2010, the Institute of Immunology Inc in Croatia from 2011-2014, and VINS Bioproducts Limited in India as of 2014.⁹⁰⁰ Nevertheless, although far from the glory days of Connaught Labs, Canada has in recent years been on the lips of those partaking in international discussions around the global DAT supply, albeit in a less overtly credible form. A Canadian company, Intervax Ltd., has periodically popped up as an ostensible international DAT distributor.⁹⁰¹ Intervax is also occasionally listed in some sources as not merely a distributor but a producer of DAT, though evidence

⁸⁹⁷ US Department of Health and Human Services, (*Healthcare Provider Letter re: DAT*) (2020).

⁸⁹⁸ Wilson, W H. "The serum dash to Nome, 1925: the making of Alaskan heroes" (1986) 16 *Alaska J* 250–259. Per the Internet Movie Database (IMDB), the two 2019 films based on these events are *Togo* and *The Great Alaskan Race*. This is a rare instance where the author cannot claim to have thoroughly investigated all these pop-cultural sources, though he vaguely remembers watching *Balto*, the 1995 animated recounting of the story, while babysitting circa the time of its release.

⁸⁹⁹ See e.g., Alberta Health Services, *Alberta Public Health Disease Management Guidelines Diphtheria* (Government of Alberta, 2019), online <<https://open.alberta.ca/publications/diphtheria>>; Ontario Ministry of Health and Long-Term Care, *Diphtheria Guide for Health Care Professionals* (Government of Ontario, 2018), online:

<http://www.health.gov.on.ca/en/pro/publications/disease/docs/Diphtheria_Guide_042018.pdf>.

⁹⁰⁰ It is unclear if any DAT has been acquired since this document was updated in 2019. Alberta Health Services, "History of Immunization in Alberta" (19 July 2019), online: <<https://open.alberta.ca/dataset/aip/resource/caab9cec-229c-4b72-a77f-9a0364167871/download/aip-history-alberta-biologicals.pdf>>.

⁹⁰¹ See e.g., Wagner, KS et al. "A review of the international issues surrounding the availability and demand for diphtheria antitoxin for therapeutic use" (2009) 28:1 *Vaccine* 14–20, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0264410X09014418>>.

supporting this assertion is minimal.⁹⁰² As of 2021, the Intervax website only offers a logo and an email address; previous cached versions do offer DAT for sale, but it is unclear where it was actually produced or where, if anywhere, it was approved.⁹⁰³ That anyone would seriously consider a small Canadian company distributing a product of indeterminate origin and approval underscores the need for a stable, transparent global supplier of assured quality. It also highlights another key theme of this thesis: that of a small, potentially unreliable company playing an outsize role in the market for an Essential Medicine.

Still, when it is needed, DAT is so vital that among those looking towards Intervax were humanitarian organizations such as MSF.⁹⁰⁴ This is because while even a single death was enough to attract headlines (if not, in the end, remedial action) in Western Europe, larger outbreaks have been occurring elsewhere to less attention; this too underscores the neglect of diphtheria. For instance, a major outbreak among Rohingya refugees in Bangladesh beginning in 2017 required access to DAT.⁹⁰⁵ Within the past decade, other outbreaks where DAT has been unavailable have had high mortality rates, demonstrating the need for ongoing access.⁹⁰⁶ In light of such events, there have been further attempts to map out the global DAT market; for instance, at a meeting in 2017, the WHO determined that meeting global needs would require between 4000 and 8000 courses of DAT treatment annually.⁹⁰⁷ However, the WHO was only able to confirm that two companies worldwide had current production capacity (though not whether they

⁹⁰² See e.g., European Centre for Disease Prevention and Control, *Gap analysis on securing diphtheria diagnostic capacity and diphtheria antitoxin availability in the EU/EEA*. (LU: Publications Office, 2017) at p.17. However, note the lack of tangible information about the company or the supply.

⁹⁰³ “Products – Antitoxins”, Intervax.com (cached version – 16 August 2018), online: <<https://web.archive.org/web/20180816145243/http://www.intervax.com/index.php/antitoxins.html>>.

⁹⁰⁴ Jason Nickerson, Personal Communication, October 30/2020.

⁹⁰⁵ Eisenberg, Nell et al., “Diphtheria Antitoxin Administration, Outcomes, and Safety: Response to a Diphtheria Outbreak in Cox’s Bazar, Bangladesh” (2020) *Clinical Infectious Diseases* ciaa1718, online: <<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1718/6007567>>.

⁹⁰⁶ See e.g., Besa, N C et al., “Diphtheria outbreak with high mortality in northeastern Nigeria” (2014) *142:4 Epidemiol Infect* 797–802.

⁹⁰⁷ World Health Organization, *Diphtheria anti-toxin (DAT) supply issues: brief review and proposition* (2017), online: <https://www.who.int/immunization/sage/meetings/2017/april/3_Diphtheria_anti_toxin.pdf>.

were actively producing DAT); another three possible producers did not even respond to WHO inquiries.⁹⁰⁸

Dwindling access to DAT also occurs against the backdrop of other shifts that could increase vulnerability to a global resurgence of the disease, including in HICs where diphtheria is largely forgotten. Here, climate change is not the culprit. In recent decades, anti-vaccination sentiments have attained a high profile in many HICs, fueled by material like the discredited (albeit only belatedly retracted) work of disgraced former physician Andrew Wakefield, who fraudulently connected the childhood MMR (measles-mumps-rubella) vaccination to autism.⁹⁰⁹ As a result of this and a variety of other unjustified claims, children all around the world have been left unvaccinated or under-vaccinated despite the ready availability of vaccines, leaving them vulnerable once again to the return of once-common diseases.⁹¹⁰ COVID-19 has served to fuel similar anti-vaccine sentiments in some quarters, suggesting the situation could deteriorate even further.⁹¹¹

This needless vulnerability is coupled with an increasingly globalized world that poses a risk of importation across borders, as has been seen with other vaccine-preventable childhood diseases like measles.⁹¹² A 2019 news report described how there had been only 17 cases of diphtheria reported in Canada between 1996 and 2016; the fact, however, that said news story was reporting a confirmed case at an Edmonton school, along with three confirmed carriers among

⁹⁰⁸ World Health Organization, *Diphtheria anti-toxin (DAT) supply issues: brief review and proposition* (2017), online:

<https://www.who.int/immunization/sage/meetings/2017/april/3_Diphtheria_anti_toxin.pdf>.

⁹⁰⁹ Eggertson, Laura, “Lancet retracts 12-year-old article linking autism to MMR vaccines” (2010) 182:4 CMAJ E199-200.

⁹¹⁰ Though it should be acknowledged that vaccines have had their opponents for as long as there have been vaccines. For but one Canadian example, see Berman, Jonathan M, “When antivaccine sentiment turned violent: the Montréal Vaccine Riot of 1885” (2021) 193:14 CMAJ E490–E492, online: <<http://www.cma.ca/lookup/doi/10.1503/cma.202820>>.

⁹¹¹ While beyond the scope of this thesis, use of legal tools like requiring vaccination as a prerequisite for children to attend school varies considerably across Canada; in a long-standing state of affairs, only Ontario and New Brunswick require diphtheria vaccination. See e.g., Walkinshaw, Erin, “Mandatory vaccinations: The Canadian picture” (2011) 183:16 CMAJ E1165-1166.

⁹¹² Sherrard, L et al., “Measles surveillance in Canada: 2015” (2016) 42:7 Can Commun Dis Rep 139–145; Sanyaolu, Adekunle et al., “Measles Outbreak in Unvaccinated and Partially Vaccinated Children and Adults in the United States and Canada (2018-2019): A Narrative Review of Cases” (2019) 56 Inquiry 46958019894098.

that case's contacts, serves as a reminder that the disease still has the potential to emerge in unexpected places and with little warning.⁹¹³ Indeed, from 2017-2019, Canada reported 22 cases, a dramatic rise that has attracted little attention and even less explanation.⁹¹⁴ As noted earlier, there has been at least one fatal case of diphtheria in Canada even since this latter reporting period.⁹¹⁵

Like most of the diseases examined in this thesis, diphtheria is also a disease that can linger longest in vulnerable communities. For instance, a 1984 examination of diphtheria in North America acknowledged that the disease had largely disappeared even by that date; at the same time, it remarked upon the fact that the "majority of cases have been either in young native people in certain rural areas, particularly northern Canada, or among middle-aged destitute males in the centre of cities, notably Seattle and Vancouver".⁹¹⁶ Similar cases were detected in Vancouver's urban poor decades later.⁹¹⁷ Such vulnerabilities may also indicate populations ripe for resurgence under the right conditions. Worldwide, major outbreaks have recently been concentrated primarily in places of conflict, unrest and population displacement, like Bangladesh, Venezuela and Yemen, but could yet spill over into other populations.⁹¹⁸

All of this hammers home the fact that as long as diphtheria exists, there will be a need for ongoing access to DAT. But while the market for DAT has changed considerably in recent decades, this Essential Medicine is still produced – when it is

⁹¹³ "3 carriers identified after confirmed case of diphtheria at Edmonton school", *CBC News* (13 June 2019), online: <<https://www.cbc.ca/news/canada/edmonton/3-diphtheria-carriers-identified-edmonton-1.5174337>>.

⁹¹⁴ Public Health Agency of Canada, "Reported cases from 1924 to 2019 in Canada - Notifiable diseases on-line", online: <<https://diseases.canada.ca/notifiable/charts?c=pl>>.

⁹¹⁵ Cholewa, Scott et al., "Fatal respiratory diphtheria in a visitor to Canada" (2021) 193:1 *CMAJ* E19–E22, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.200707>>.

⁹¹⁶ Though these cases were generally of the cutaneous (rather than the more dangerous nasopharyngeal, form. Dixon, J M. "Diphtheria in North America" (1984) 93:3 *The Journal of Hygiene* 419–432.

⁹¹⁷ Lowe, C F, K A Bernard & M G Romney, "Cutaneous Diphtheria in the Urban Poor Population of Vancouver, British Columbia, Canada: a 10-Year Review" (2011) 49:7 *J Clin Microbiol* 2664–2666, online: <<https://jcm.asm.org/content/49/7/2664>>.

⁹¹⁸ Blumberg, LH et al., "The preventable tragedy of diphtheria in the 21st century" (2018) 71 *International Journal of Infectious Diseases* 122–123, online:

<<https://linkinghub.elsevier.com/retrieve/pii/S1201971218344102>>;

Clarke, Kristie E N et al., "Global Epidemiology of Diphtheria, 2000-2017" (2019) 25:10 *Emerg Infect Dis* 1834–1842.

produced at all – in the way it was at the tail end of the 19th Century: The diphtheria toxin is injected into a horse, whose immune system responds by generating antibodies/antitoxins.⁹¹⁹ In turn, the serum that results can be extracted from the horse, purified, and given to the human patient.⁹²⁰ Such serum products are more difficult to standardize and to regulate; they also require certain resources no longer the norm in pharmaceutical manufacturing, such as the capacity to care for a sufficient number of large ungulates. That a commercially unattractive drug can only be produced via commercially unattractive means exacerbates the problem of relying upon commercial considerations to ensure its supply.⁹²¹ The disappearance of a global supply means outbreaks in conflict and disaster settings are becoming deadlier than they would have been, while deaths have needlessly occurred even in HICs as the world is left scrambling for access. The fact that even HICs have ultimately settled for expired stocks, or for obtaining unapproved supplies from potentially dubious sources, illustrates that ostensible concern for regulatory standards ultimately and inevitably yields to the need for access to Essential

⁹¹⁹ Kupferschmidt, Kai, “Life-saving diphtheria drug is running out” (2017) 355:6321 *Science* 118–119, online: <<https://www.sciencemag.org/lookup/doi/10.1126/science.355.6321.118>>.

⁹²⁰ DAT has been made from other sources, including human plasma, but never in sufficient quantity to meet the necessary demand. See e.g., World Health Organization, *Diphtheria anti-toxin (DAT) supply issues: brief review and proposition* (2017), online: <https://www.who.int/immunization/sage/meetings/2017/april/3_Diphtheria_anti_toxin.pdf>.

⁹²¹ Despite a lack of commercial interest in DAT, it is not impossible that an improved method of production could emerge, were it given – and this is an important caveat – sufficient resources and attention. As illustrated at various junctures thus far, a surge of interest in researching treatments for disease can be motivated by many things, from colonialism to combat. For DAT, a resurgence in research interest has come from an unanticipated source – the activist group PETA (People for the Ethical Treatment of Animals). People for the Ethical Treatment of Animals (PETA), “Press Release - Scientists show we don't need horses to treat diphtheria”, (21 January 2020), online: <<https://www.peta.org/media/news-releases/scientists-show-we-dont-need-horses-to-treat-diphtheria/>>. Their interest in reforming this 19th Century technique is rooted in concern about the treatment of the horses. Early results of a PETA-funded project to use human blood cells in a laboratory setting to generate human antibodies against diphtheria toxin have shown some promise. Wenzel, Esther Veronika et al., “Human antibodies neutralizing diphtheria toxin in vitro and in vivo” (2020) 10:1 *Sci Rep* 571, online: <<http://www.nature.com/articles/s41598-019-57103-5>>. Others have proposed methods along similar lines. Bermejo-Martin, Jesús F et al., “Postbooster Antibodies from Humans as Source of Diphtheria Antitoxin” (2016) 22:7 *Emerg Infect Dis* 1265–1267. Nonetheless, a horse-free approach is still a long way from providing a solution to the DAT access issue; furthermore, given the lack of attention to DAT, and to diphtheria in general, it is unclear how it might attract sufficient funding to conduct human trials and ultimately bring the product to market, particularly if commercial producers must be relied upon. Kupferschmidt, Kai, “Life-saving diphtheria drug is running out” (2017) 355:6321 *Science* 118–119, online: <<https://www.sciencemag.org/lookup/doi/10.1126/science.355.6321.118>>.

Medicines. Unfortunately, no party has stepped in to effectively fill the void left by the market. At this stage, it seems virtually impossible that any individual country could support a sustainable commercial market on its own; nevertheless, the strategy of virtually every country seems to be to hope that such a supply will exist, somewhere else in the world, at the time it is needed. This underscores the need for international collaboration to ensure ongoing production of Essential Medicines as a matter of both the global common good and enlightened self-interest. As yet, this issue has not received the attention it requires.

Antimicrobial resistance

Even as access to off-patent Essential Medicines receives less attention at the national and international level than it merits, it implicates other health issues with global ramifications whose profile is increasing. One such area is Antimicrobial Resistance (AMR).⁹²² The relationship between Essential Medicines and AMR is multifaceted. For instance, the utility of numerous existing Essential Medicines for Neglected Diseases is threatened by emerging AMR; in fact, numerous drugs on the WHO MEML, from cycloserine to artemisinin-based treatments for malaria, are Essential Medicines in large part because they treat diseases now resistant to other drugs. As AMR evolves, the efficacy of these Essential Medicines may decrease in turn. The dearth of new treatments for Neglected Diseases overlaps with the pharmaceutical industry's broader shift away from developing new antibiotics, with many major pharmaceutical companies no longer involved in this area at all.⁹²³ This lack of commercial interest is itself affected by how patterns of antibiotic use are shifting; in order to preserve its utility, any new antibiotic entering the market will most likely be used sparingly, meaning that the prospects of high-volume sales are low.⁹²⁴ At the same time, a focus on new antimicrobials to combat

⁹²² "Antimicrobial resistance: a top ten global public health threat" (2021) 41 EClinicalMedicine 101221.

⁹²³ Plackett, Benjamin, "Why big pharma has abandoned antibiotics" (2020) 586:7830 Nature S50–S52, online: <<http://www.nature.com/articles/d41586-020-02884-3>>.

⁹²⁴ Cogan, Deirdre, Karrar & Jayasree K Iyer. *Shortages, stockouts and scarcity: The issues facing the security of antibiotic supply and the role for pharmaceutical companies*, White Paper (Access to Medicine Foundation, 2018), online:

drug-resistant pathogens should also not overshadow the fact that access to existing antimicrobials is connected to the emergence of AMR in the first place. As the very existence of MDR-TB and XDR-TB aptly illustrate, AMR is a problem that originates not from the failure to develop effective medicines in the first place, but a failure to utilize those medicines optimally.⁹²⁵

The international response to AMR is today an area where Essential Medicines lists are both being adapted (via producing lists of particularly important medicines of a specific kind) and directly integrated (by means of the WHO MEML itself). For instance, since 2005, the WHO has published a regularly updated list of *Critically Important Antimicrobials for Human Medicine* (WHO CIA List), which classifies antimicrobials into 3 categories: Critically Important, Highly Important and Important.⁹²⁶ The WHO CIA List not only draws from the Essential Medicines concept, but is intended to be used in conjunction with the WHO MEML itself, alongside other lists like the OIE (World Organization for Animal Health) list of antimicrobials of veterinary importance.⁹²⁷ In turn, since 2017 the WHO MEML itself has also categorized antibiotics into three groups – Access (to improve access), Watch (to monitor) and Reserve (preserve as “last resort” antibiotics) – a classification system known as AWaRe.⁹²⁸ Building upon this further, the WHO has also since launched a broader AWaRe Classification Database, which expands these

<<https://accessmedicinefoundation.org/publications/shortages-stockouts-and-scarcity-the-issues-facing-the-security-of-antibiotic-supply-and-the-role-for-pharmaceutical-companies>>.

⁹²⁵ The problem of drug resistance has been recognized for a long time in the context of TB treatment. By the time Selman Waksman earned the Nobel Prize in Physiology or Medicine in 1952 “for his discovery of streptomycin, the first antibiotic effective against tuberculosis,” the risks of the rapid development of streptomycin resistance had already been known for years. The Nobel Prize in Physiology or Medicine 1952”, online: *NobelPrize.org*

<<https://www.nobelprize.org/prizes/medicine/1952/summary/>>; Hinshaw, Corwin, Marjorie M Pyle & William H Feldman, “Streptomycin in tuberculosis” (1947) 2:5 *The American Journal of Medicine* 429–435, online: <<https://linkinghub.elsevier.com/retrieve/pii/0002934347900879>>.

⁹²⁶ World Health Organization, *Critically Important Antimicrobials for Human Medicine*, 6th Revision (World Health Organization, 2019).

⁹²⁷ World Health Organization, *Critically Important Antimicrobials for Human Medicine*, 6th Revision (World Health Organization, 2019) at p.7.

⁹²⁸ Gulland, Anne, “WHO targets antimicrobial resistance in new essential medicines list” (2017) *BMJ* j2809, online: <<https://www.bmj.com/lookup/doi/10.1136/bmj.j2809>>; Sharland, Mike et al., “Classifying antibiotics in the WHO Essential Medicines List for optimal use—be AWaRe” (2018) 18:1 *The Lancet Infectious Diseases* 18–20, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1473309917307247>>.

classifications to include antibiotics not found on the WHO MEML.⁹²⁹ By integrating AMR considerations directly into the WHO MEML, medical utility and separate but related considerations such as preserving that medical utility by preventing the emergence of AMR can be addressed using the same tool. This means access to an Essential Medicine might be simultaneously promoted and restricted, with Essential Medicine status for a particular indication counterbalanced by limitations on other uses to protect the continued usefulness of the drug for that Essential indication.

Like the underlying MEML, these AMR classifications can then influence law and policy at the international, national or subnational level. Indeed, the past decade has seen not merely a flurry of policy and guidance at the international level, but a discussion of developing binding international legal instruments, such as the idea of an AMR treaty.⁹³⁰ Canada too draws upon the AWaRe classifications in its own domestic AMR analysis.⁹³¹ AMR has spurred both soft law and hard law tools domestically as well. For example, in 2009, Canada developed a guidance document on “Categorization of Antimicrobial Drugs Based on Importance in Human Medicine” that identified categories of medicines.⁹³² By 2017, it had amended the *Food and Drug Regulations* to place a legal prohibition on the non-

⁹²⁹ The 2019 AWaRe Classification Database classifies 48 drugs (including 19 Essential Medicines) in the Access category, 110 (including 11 Essential Medicines) in the Watch category, and 22 (including 7 Essential Medicines) in the Reserve category. World Health Organization, “WHO releases the 2019 AWaRe Classification Antibiotics” (1 October 2019), online: <<https://www.who.int/news/item/01-10-2019-who-releases-the-2019-aware-classification-antibiotics>>.

⁹³⁰ See e.g., Hoffman, Steven J et al., “An international legal framework to address antimicrobial resistance” (2015) 93:2 Bull World Health Organ 66; Padiyara, Ponnu, Hajime Inoue & Marc Sprenger, “Global Governance Mechanisms to Address Antimicrobial Resistance” (2018) 11 Infect Dis (Auckl).

⁹³¹ Public Health Agency of Canada, *Canadian Antimicrobial Resistance Surveillance System Report 2021*, (Ottawa: Health Canada, 2021), online: <<https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-report-2021/canadian-antimicrobial-resistance-surveillance-system-report-2021.pdf>>.

⁹³² Notably, it includes tuberculosis treatments in Category 1: Very High Importance. Health Canada, “Categorization of Antimicrobial Drugs Based on Importance in Human Medicine”, (2009), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/antimicrobial-resistance/categorization-antimicrobial-drugs-based-importance-human-medicine.html>>.

prescription sale for veterinary use of a specified list of antibiotics.⁹³³ This are further demonstrations of how a list of drugs can have legal implications at the domestic level in Canada.

Nevertheless, even as the broader issue of AMR garners more attention, and contributing factors like excessive use of antibiotics in areas like agriculture are tackled, one vital component of the issue is not receiving its full due, either at home or internationally: ensuring that the appropriate drugs are available in the first place.⁹³⁴ Lack of access has implications for AMR; part of proper antibiotic stewardship is not simply avoiding the wrong drug at the wrong time, but having access to the right drug at the right time.⁹³⁵ As Pulcini and colleagues noted close to a decade ago, “Several older, potentially useful, sometimes ‘forgotten’ antibiotics are not available in many countries, either never having been introduced or having now been withdrawn”.⁹³⁶ The consequences include access issues in HICs. A 2011 survey conducted across Canada, the United States, Australia and 35 European nations focused on the availability of 33 antibiotics selected by an international expert panel for their potential to treat infections caused by resistant bacteria or their unique value for other specific criteria.⁹³⁷ It found that 22 of the 33 selected antibiotics were available in fewer than 20 of 38 countries.⁹³⁸ The authors also found that economic motives were the major cause of discontinuation for these

⁹³³ “Regulations Amending the Food and Drug Regulations (Veterinary Drugs — Antimicrobial Resistance),” *Canada Gazette* (17 May 2017) Vol. 151, No. 10, online: <<https://gazette.gc.ca/rp-pr/p2/2017/2017-05-17/html/sor-dors76-eng.html>>.

⁹³⁴ Cogan, Deirdre, Karrar & Jayasree K Iyer. *Shortages, stockouts and scarcity: The issues facing the security of antibiotic supply and the role for pharmaceutical companies*, White Paper, by Deirdre Cogan, Karrar & Jayasree K Iyer, White Paper (Access to Medicine Foundation, 2018).

⁹³⁵ See e.g., Daulaire, Nils et al., “Universal Access to Effective Antibiotics is Essential for Tackling Antibiotic Resistance” (2015) 43 Suppl 3 J Law Med Ethics 17–21.

⁹³⁶ Pulcini, Céline et al. “Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia” (2012) 54:2 Clinical Infectious Diseases 268–274, online: <<https://academic.oup.com/cid/article/54/2/268/471278>>.

⁹³⁷ Pulcini, Céline et al. “Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia” (2012) 54:2 Clinical Infectious Diseases 268–274, online: <<https://academic.oup.com/cid/article/54/2/268/471278>>.

⁹³⁸ Pulcini, Céline et al. “Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia” (2012) 54:2 Clinical Infectious Diseases 268–274, online: <<https://academic.oup.com/cid/article/54/2/268/471278>>.

drugs.⁹³⁹ The result is an issue already seen with Essential Drugs for Neglected Diseases: “Many of the older antibiotics are now only produced by pharmaceutical industries in developing nations, which may further impede the access to these drugs, because there may be a lack of influence of regulatory bodies in Europe and elsewhere”.⁹⁴⁰ The authors conclude that “policy makers are well advised to guarantee the availability of older and generic antibiotics and other drugs that are essential for medical care, beyond market-driven agendas”.⁹⁴¹

A follow-up study a few years later found the situation slightly worsening. Once again, the authors indicated that the “underlying reasons seem mainly economic in addition to lack of awareness and priority among health authorities”.⁹⁴² They concluded that “existing and useful antibiotics are less and less available to clinicians in Europe, the USA, Canada and Australia, and the situation has worsened since our last survey in 2011” and that “International measures are urgently needed, and access and responsible use should be as much a priority as innovation in the public debate”.⁹⁴³ Related concerns have been flagged elsewhere; for instance, an American study looking at antibiotic shortages between 2001 and 2013 found that 148 antibacterial drugs were in shortage over the study period; of these 73 (or 49% of the total) “were listed as having no alternative production source”.⁹⁴⁴ Even where such drugs are currently on the market, they are vulnerable to shortages, to potential exploitation, and to leaving the market

⁹³⁹ Pulcini, Céline et al. “Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia” (2012) 54:2 *Clinical Infectious Diseases* 268–274, online: <<https://academic.oup.com/cid/article/54/2/268/471278>>.

⁹⁴⁰ Pulcini, Céline et al. “Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia” (2012) 54:2 *Clinical Infectious Diseases* 268–274, online: <<https://academic.oup.com/cid/article/54/2/268/471278>>.

⁹⁴¹ Pulcini, Céline et al. “Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia” (2012) 54:2 *Clinical Infectious Diseases* 268–274, online: <<https://academic.oup.com/cid/article/54/2/268/471278>>.

⁹⁴² Pulcini, Céline et al. “Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia” (2017) 49:1 *International Journal of Antimicrobial Agents* 98–101, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0924857916303363>>.

⁹⁴³ Pulcini, Céline et al. “Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia” (2017) 49:1 *International Journal of Antimicrobial Agents* 98–101, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0924857916303363>>.

⁹⁴⁴ Quadri, F et al. “Antibacterial Drug Shortages From 2001 to 2013: Implications for Clinical Practice” (2015) 60:12 *Clinical Infectious Diseases* 1737–1742, online: <<https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/civ201>>.

entirely. Not all of these antibiotics are Essential Medicines, of course, but some of them are; in turn, the absence of one drug places pressure on those drugs that remain available, fomenting the risk of perpetuating the development of further drug resistance. In an ironic twist, Canada's lack of a domestic EML led to its omission from recent Canadian-led research into the alignment of the AWaRe classification with national EMLs across 138 countries, illustrating another potential use for such a tool.⁹⁴⁵

This thesis has already highlighted the fact that less than half the drugs for drug-resistant tuberculosis included in the last version of Canadian treatment guidelines are formally available in Canada, despite the fact all of them were on the WHO MEML at the time. To give another concrete Canadian example of how AMR, Essential Medicines and access mechanisms for unmarketed drugs intersect, consider the official Canadian Guidelines on Sexually Transmitted Infections.⁹⁴⁶ In 2017, an update was issued on the treatment of gonorrhea (a sexually transmitted infection that may not be a Neglected Disease, but is certainly an undesirable one). It provided a shift in treatment guidance after noting that PHAC "has been informed that manufacturing of spectinomycin has been discontinued".⁹⁴⁷ Underscoring the absurdity of the situation, the discontinuation referred to by PHAC was not from the Canadian market, but *of a foreign source*; by this point, Canadian spectinomycin access had been reliant on the SAP for two decades, after the only Canadian manufacturer discontinued the product in 1997.⁹⁴⁸ Now, twenty years later, as a

⁹⁴⁵ Adekoya, Itunuoluwa et al., "Comparison of antibiotics included in national essential medicines lists of 138 countries using the WHO Access, Watch, Reserve (AWaRe) classification: a cross-sectional study" (2021) 21:10 The Lancet Infectious Diseases 1429–1440, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1473309920308549>>.

⁹⁴⁶ Health Canada, "Canadian Guidelines on Sexually Transmitted Infections" (no date), online: <<https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections.html>>.

⁹⁴⁷ Health Canada, "Treatment of N. gonorrhoeae in response to the discontinuation of spectinomycin: Alternative treatment guidance statement" *Canadian Guidelines on Sexually Transmitted Infections* (July 2017 Update), online: <<https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/healthy-living/gonorrhea-alternate-treatment/alternate-treatment-gonorrhea-07-2017.pdf>>.

⁹⁴⁸ Health Canada, "Treatment of N. gonorrhoeae in response to the discontinuation of spectinomycin: Alternative treatment guidance statement" *Canadian Guidelines on Sexually Transmitted Infections* (July 2017 Update), online: <<https://www.canada.ca/content/dam/phac>>.

result of a foreign discontinuation, this drug was “no longer available through Health Canada’s Special Access Program (SAP)”.⁹⁴⁹ PHAC warned that “[i]n the face of increasing antimicrobial resistance in *Neisseria gonorrhoeae*, the discontinuation of spectinomycin has the potential to limit gonorrhea prevention and control efforts in Canada by further restricting treatment options”.⁹⁵⁰ Ironically, spectinomycin, a drug developed in the 1960s, had been added to the WHO MEML the same year as this PHAC update, under the AWaRe classification of “access”.⁹⁵¹

This tale of Canadian access to a drug recommended in official Canadian guidelines being premised entirely on accessing an unapproved foreign supply of a drug long discontinued in Canada does not end here, even within the same set of guidelines for the treatment of gonorrhea. One of the alternatives to spectinomycin suggested by PHAC in this 2017 update is gemifloxacin; the sole market authorization holder in Canada had discontinued gemifloxacin in 2009. Furthermore, the update itself notes that “at the time of publication, gemifloxacin was not available on the Canadian or US market” but suggests that in “the future, gemifloxacin is expected to be marketed in the US, at which time it will be made accessible through Health Canada’s Special Access Program (SAP)”.⁹⁵² To summarise this multi-layered access fiasco: two drugs, one an Essential Medicine,

aspc/documents/services/publications/healthy-living/gonorrhea-alternate-treatment/alternate-treatment-gonorrhea-07-2017.pdf>.

⁹⁴⁹ Health Canada, “Treatment of N. gonorrhoeae in response to the discontinuation of spectinomycin: Alternative treatment guidance statement” *Canadian Guidelines on Sexually Transmitted Infections* (July 2017 Update), online: <<https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/healthy-living/gonorrhea-alternate-treatment/alternate-treatment-gonorrhea-07-2017.pdf>>.

⁹⁵⁰ Health Canada, “Treatment of N. gonorrhoeae in response to the discontinuation of spectinomycin: Alternative treatment guidance statement” *Canadian Guidelines on Sexually Transmitted Infections* (July 2017 Update), online: <<https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/healthy-living/gonorrhea-alternate-treatment/alternate-treatment-gonorrhea-07-2017.pdf>>.

⁹⁵¹ WHO Expert Committee on the Selection and Use of Essential Medicines, ed, *The selection and use of essential medicines: report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children)*, WHO technical report series 1006 (Geneva: WHO, 2017).

⁹⁵² Health Canada, “Treatment of N. gonorrhoeae in response to the discontinuation of spectinomycin: Alternative treatment guidance statement” *Canadian Guidelines on Sexually Transmitted Infections* (July 2017 Update), online: <<https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/healthy-living/gonorrhea-alternate-treatment/alternate-treatment-gonorrhea-07-2017.pdf>>.

found in Canada's official treatment guidelines for gonorrhea had both been discontinued from the Canadian market years before, leaving access dependent on obtaining an unapproved foreign source via the SAP; subsequently, access via the SAP was jeopardized when the key foreign sources of both drugs became unavailable, with official recommendations essentially invoking a crossing of fingers for one of the drugs to reappear on the market in the United States. This illustrates just how precarious access to old antimicrobials can be, even when their public health importance is clear.⁹⁵³

Finally, antibiotics offer another example of how high-income countries can be serve as harbingers for wider access issues, as domestic market shortages become global market absences. While global production of some Essential Medicines may be sustainable based primarily on widespread use in lower-income countries, this is not always the case. A particularly prominent example, with major global repercussions, involves recent shortages of the Essential Medicine benzathine penicillin G (BPG; also known as benzathine benzylpenicillin). Although BPG is currently marketed in Canada, the number of suppliers has decreased considerably over the past few decades, leaving only one today; Canada has also faced multiple serious shortages during this time. Here, Canada's experience reflects broader trends in the global BPG supply, where access to an Essential Medicine is threatened in HICs and LMICs alike. This is a reminder that identifying medicines as Essential is not a solution in and of itself; steps must be taken proactively to ensure sustainable access.

Access to BPG

Penicillin has been called "the single greatest victory ever achieved over disease".⁹⁵⁴ Discovered by Alexander Fleming in 1928, it was the first modern

⁹⁵³ A slight silver lining is that the crossing of fingers seems to have worked, as a source of gemifloxacin is once again approved in the United States. This still doesn't vindicate finger-crossing as a reliable strategy.

⁹⁵⁴ Bennett, Joan W & King-Thom Chung, "Alexander Fleming and the discovery of penicillin" in *Advances in Applied Microbiology* (Elsevier, 2001) at p.163.

antibiotic.⁹⁵⁵ It will come as no surprise that penicillin yielded a Nobel Prize; it should be noted, however, that Fleming shared the honours with Ernst B. Chain and Sir Howard Florey for their work on a form of the drug that could be systematically produced in large quantities.⁹⁵⁶ Thus, the Nobel Prize for penicillin recognized the importance not merely of the creation of a drug, but of the means for ensuring widespread access to it. Today, multiple kinds of penicillin exist, including the WHO MEML-listed BPG. BPG remains a gold standard treatment for syphilis; it is particularly important for prevention of congenital syphilis, for which other regimens may be dangerous or ineffective.⁹⁵⁷ As such, BPG is not only an Essential Medicine for treatment generally, but also a vital public health tool for achieving the goal of ending mother-to-child transmission of the disease.⁹⁵⁸ This is an important consideration in Canada, where syphilis is another disease once thought vanquished that has been on the rise in recent years, including a resurgence of the congenital cases previously considered to be a thing of the past.⁹⁵⁹ Indeed, in 2021, Alberta's Chief Medical Officer of Health went so far as to suggest that devoting public health resources to COVID-19 had come at "the cost of not fully working on

⁹⁵⁵ Fleming, Alexander, "On the Antibacterial Action of Cultures of a *Penicillium*, with Special Reference to their Use in the Isolation of *B. influenzae*" (1929) 10:3 *The British Journal of Experimental Pathology* 226–236. The word antibiotic is qualified with the word "modern" to rule out other obsolete contenders like Paul Ehrlich's then-breakthrough syphilis treatment Salvarsan, a drug notable in the context of this thesis for stemming from research to develop a less toxic arsenical drug than the previously discussed African trypanosomiasis drug Atoxyl. See e.g., Thorburn, A L, "Paul Ehrlich: pioneer of chemotherapy and cure by arsenic (1854-1915)" (1983) 59:6 *Br J Vener Dis* 404–405.

⁹⁵⁶ "The Nobel Prize in Physiology or Medicine 1945", online: *NobelPrize.org* <<https://www.nobelprize.org/prizes/medicine/1945/summary/>>.

⁹⁵⁷ Clement, Meredith E, N Lance Okeke & Charles B Hicks, "Treatment of syphilis: a systematic review" (2014) 312:18 *JAMA* 1905–1917.

⁹⁵⁸ World Health Organization, *Global guidance on criteria and processes for validation: Elimination of Mother-to-Child Transmission of HIV and Syphilis*, 2nd ed (World Health Organization, 2017); Taylor, Melanie M et al., "The amount of penicillin needed to prevent mother-to-child transmission of syphilis" (2016) 94:8 *Bull World Health Organ* 559–559A, online: <<http://www.who.int/entity/bulletin/volumes/94/8/16-173310.pdf>>.

⁹⁵⁹ Choudhri, Y et al., "Infectious and congenital syphilis in Canada, 2010–2015" (2018) 44:2 *Canada Communicable Disease Report* 43–48, online: <<https://www.canada.ca/content/dam/phac-aspc/documents/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/>>; Robinson, JL, "Congenital syphilis: No longer just of historical interest" (2009) 14:5 *Paediatrics & Child Health*, online: <<http://academic.oup.com/pch/article/14/5/337/2639302/Paediatric-Infectious-Disease-Notes>>. 2018-44/issue-2-february-1-2018/ccdrv44i02a02-eng.pdf>.

other threats, like syphilis” in justifying the roll-back of provincial public health measures in response to the pandemic.⁹⁶⁰

At the international level, BPG plays an additional important role in addressing rheumatic fever (RF) and rheumatic heart disease (RHD) – a key cause of acquired heart disease in young people – resulting from group A streptococcal infections. This has long been recognized as another once-prevalent condition that has mostly vanished from high-income countries.⁹⁶¹ While largely eliminated from Canada, it remains a concern in certain populations, including some remote Indigenous communities.⁹⁶² When it comes to treating RF, maintaining access to BPG is important, as missing “even a single dose of BPG raises the risk of recurrent RF and can undermine entire secondary prophylaxis programs”.⁹⁶³ Unfortunately, in a story by now familiar to the reader, “as rheumatic heart disease has receded as a public health priority in most high-income settings, attention to the supply, manufacture, and accessibility of benzathine penicillin G has declined”.⁹⁶⁴

BPG has further characteristics putting it at risk of shortage that will at this point also seem familiar. As a sterile injectable medication, it is more complex and more expensive to manufacture; this is both a disincentive to market entry for new suppliers and a contributor to existing suppliers shifting production towards less resource-intensive and more commercially appealing products.⁹⁶⁵ Since the early

⁹⁶⁰ Hinshaw, Deena, “Learning to live with COVID-19” (4 August 2021), Government of Alberta, online: <<https://www.alberta.ca/article-learning-to-live-with-covid-19.aspx>>.

⁹⁶¹ See e.g., Dodu, S R & S Böthig, “Rheumatic fever and rheumatic heart disease in developing countries” (1989) 10:2 World Health Forum 203–212.

⁹⁶² Gordon, Janet et al., “Acute rheumatic fever in First Nations communities in northwestern Ontario: Social determinants of health ‘bite the heart’” (2015) 61:10 Can Fam Physician 881–886; Madden, Sharen & Len Kelly, “Update on acute rheumatic fever: it still exists in remote communities” (2009) 55:5 Can Fam Physician 475–478. Moreover, there have been occasional outbreaks in other contexts in the not so distant past, e.g., Wong, D, R Bortolussi & B Lang, “An outbreak of acute rheumatic fever in Nova Scotia” (1998) 24:6 Can Commun Dis Rep 45–47.

⁹⁶³ Wyber, Rosemary et al. “Benzathine Penicillin G for the Management of RHD: Concerns About Quality and Access, and Opportunities for Intervention and Improvement” (2013) 8:3 227, online: <<https://globalheartjournal.com/article/10.1016/igheart.2013.08.011/>>.

⁹⁶⁴ Wyber, Rosemary et al. “Benzathine Penicillin G for the Management of RHD: Concerns About Quality and Access, and Opportunities for Intervention and Improvement” (2013) 8:3 227, online: <<https://globalheartjournal.com/article/10.1016/igheart.2013.08.011/>>.

⁹⁶⁵ Nurse-Findlay, Stephen et al. “Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews” (2017) 14:12 PLoS Med e1002473.

2000s, at least 6 manufacturers of the active pharmaceutical ingredient (API) and over 40 companies producing the final product have left the global market for BPG.⁹⁶⁶ In Canada, only one supplier (Pfizer) remains, leaving Canada vulnerable to shortages. According to the Health Canada Drug Product Database, most suppliers left the Canadian market, some after being there for decades, in the mid-1990s. As the number of suppliers dwindled, the 2002 decision by Wyeth-Amherst to stop producing BPG at its Canadian facility and exit the market had a particular impact, resulting in North American shortages.⁹⁶⁷ Around the world, many countries were experiencing shortages around the same time.⁹⁶⁸

Another major global shortage followed a decade later; one study found over 40% of the 95 countries surveyed had reported a BPG shortage between 2014-2016.⁹⁶⁹ The affected countries ranged from Canada and Germany to Malawi and Zimbabwe.⁹⁷⁰ In Canada, this more recent shortage made headlines, further exacerbated by domestic manufacturing issues at Pfizer Canada.⁹⁷¹ The shortage ultimately led the Public Health Agency of Canada to issue interim treatment guidelines for syphilis to preserve scarce BPG stocks for certain categories of

⁹⁶⁶ Nurse-Findlay, Stephen et al. "Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews" (2017) 14:12 PLoS Med e1002473.

⁹⁶⁷ Scolnik, D et al., "Efficacy of a Targeted, Oral Penicillin-Based Yaws Control Program among Children Living in Rural South America" (2003) 36:10 Clin Infect Dis 1232-1238, online: <<https://academic.oup.com/cid/article-lookup/doi/10.1086/374338>>; Wyber, Rosemary et al. "Benzathine Penicillin G for the Management of RHD: Concerns About Quality and Access, and Opportunities for Intervention and Improvement" (2013) 8:3 gh 227, online: <<https://globalheartjournal.com/article/10.1016/j.ghart.2013.08.011/>>.

⁹⁶⁸ See e.g., Currie, Bart, "Benzathine penicillin - down but not out" (2006) 13:2 The Northern Territory Disease Control Bulletin 1-3, online: <<https://digitalibrary.health.nt.gov.au/prodjsui/bitstream/10137/506/443/Vol.%2013%20no%202%20June%202006.pdf>>.

⁹⁶⁹ Nurse-Findlay, Stephen et al. "Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews" (2017) 14:12 PLoS Med e1002473.

⁹⁷⁰ Nurse-Findlay, Stephen et al. "Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews" (2017) 14:12 PLoS Med e1002473.

⁹⁷¹ "Syphilis drug shortage comes amid high infection rates across Canada", *CBC News* (3 May 2016), online: <<https://www.cbc.ca/news/health/syphilis-drug-shortage-1.3564467>>.

patient, such as pregnant women.⁹⁷² With the shortage classified as a Tier 3 shortage, Health Canada ultimately had to import an alternative supply from Australia; they were fortunate to find such a supply at a time of worldwide stockouts.⁹⁷³

The repercussions of global BPG shortages were sufficiently severe that the WHO Secretariat took notice, delivering a 2015 report on access to medicines explicitly highlighting the fact that BPG “has been in chronic short supply for several years”.⁹⁷⁴ The BPG supply issue was echoed in a revised version of the report, presented the following year at the 2016 World Health Assembly.⁹⁷⁵ These concerns were also spelled out in more detail in a report from RHD Action, an international NGO coalition, which highlights issues such as the shortage of API and the lack of interest by manufacturers in producing BPG.⁹⁷⁶ Meanwhile, attrition from the global market continued; by 2017, it was reported that just four companies worldwide produced the API needed to make BPG, three of which were in China.⁹⁷⁷ Concentration of production in a single country creates further potential vulnerabilities in future supply, whether due to natural disasters or geopolitical upheavals. While a 2018 WHA resolution on rheumatic fever and rheumatic heart disease calls upon a range of entities “to facilitate timely,

⁹⁷² Public Health Agency of Canada, “Interim Syphilis Treatment Guidelines during the Benzathine Penicillin G (Bicillin L-A) Shortage 2016”, online: <<https://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/assets/pdf/syphilis-eng.pdf>>.

⁹⁷³ Health Canada, *BICILLIN L-A Injection (penicillin G benzathine) 2 mL Single Use Syringe - Shortage and Replacement with Australian Labelled Stock*, by Health Canada, RA-58338 (2016).

⁹⁷⁴ WHO Secretariat, *Addressing the global shortages of medicines, and the safety and accessibility of children’s medication*, Report by the Secretariat, by WHO Secretariat, Executive Board 138th Session Report by the Secretariat EB138/41 (World Health Organization, 2015).

⁹⁷⁵ World Health Assembly, *Addressing the global shortages of medicines, and the safety and accessibility of children’s medication*, Sixty-Ninth World Health Assembly Report by the Secretariat A69/42 (World Health Organization, 2016) at para. 4.

⁹⁷⁶ RHD Action, *Global Status of BPG Report* (2016), online: <https://rhdaction.org/sites/default/files/RHD%20Action_Global%20Status%20of%20BPG%20Report_Online%20Version.pdf>.

⁹⁷⁷ Guimaraes, Keila. “Penicillin shortages as pharma companies eye newer, more lucrative drugs”, *Bhekisisa Centre for Health Journalism* (6 June 2017), online: <<http://bhekisisa.org/article/2017-05-25-penicillin-shortages-as-pharma-companies-eye-newer-more-lucrative-drugs>>.

affordable and reliable access to existing and cost-effective new medicines”, it does not offer any clear indications of how to go about doing so.⁹⁷⁸

BPG is thus a key illustration of how an off-patent Essential Medicine that continues to play an important role in global health for multiple conditions has seen its global supplies become increasingly perilous. It is available in Canada for now, but with a history of unstable access and only one supplier remaining in the market. BPG thus serves as another example of how a sustainable global supply of an off-patent Essential Medicine would have benefits for all countries. A 2021 report to the World Health Assembly by the Director-General reaches the same conclusion, noting that the WHO is working “on strategies to create a market for the use of benzathine benzylpenicillin that incentivizes its production by manufacturers and enables countries to achieve a steady, quality-assured supply” including WHO Prequalification.⁹⁷⁹ While focused on a single drug, rather than broader systemic issues that this drug represents, this is still a positive step towards recognizing the issue of continued global access to old Essential Medicines, even if as of this writing it has yet to yield results. It also offers an example of a situation where Canada should strike common cause in supporting a sustainable quality-assured global supply in a manner permitting it to shore up its own supply in the process.

⁹⁷⁸ World Health Assembly, *Rheumatic fever and rheumatic heart disease*, (World Health Organization, 2018) WHA71.14.

⁹⁷⁹ World Health Assembly, *Updates and future reporting - Rheumatic fever and rheumatic heart disease*, Report by the Director-General, A74/40 (World Health Organization, 2021).

Interlude: Essential Medicines and human rights

Before turning in earnest to solutions, it is worth taking a few pages to acknowledge an issue thus far only alluded to in this thesis. Like patents, human rights have a tendency to overshadow other considerations in the access to medicines discussion. The decision to leave them on the sidelines thus far has been an intentional one, not because they are unimportant, but to ensure they do not overwhelm the conversation. There is no shortage of scholarship on human rights and access to Essential Medicines; part of the intent of this thesis is to give overlooked areas more attention. Nonetheless, especially given their salience at the international level, it is worth briefly situating human rights within the Essential Medicines conversation. Essential Medicines have, Greene argues, joined “clean water, adequate housing and a safe food supply as part of a short list of things necessary for basic humanitarian conditions, and added the ‘right to medicines’ to the broader rights discourse of UN organizations”.⁹⁸⁰ The most important touchstone in this discourse is General Comment 14 by the UN Committee on Economic, Social and Cultural Rights (UN CESCR), and its influential characterization of the state obligation “to provide essential drugs, as from time to time defined under the WHO Action Programme on Essential Drugs” as constituting a core obligation of the Right to Health under the International Covenant on Economic, Social and Cultural Rights (ICESCR).⁹⁸¹

Not only does General Comment 14 shift the normative influence of Essential Medicines on state practice into a legally binding obligation, its characterization of access to Essential Medicines as a core human rights obligation means that unlike the progressive realization that characterizes most state obligations under the ICESCR, the provision of Essential Medicines must be realized

⁹⁸⁰ Greene, Jeremy A. “Making medicines essential: The emergent centrality of pharmaceuticals in global health” (2011) 6:1 *BioSocieties* 10–33, online: <<http://link.springer.com/10.1057/biosoc.2010.39>>.

⁹⁸¹ UN Committee on Economic, Social and Cultural Rights (CESCR), *General Comment No. 14: The Right to the Highest Attainable Standard of Health (Art. 12 of the International Covenant on Economic, Social and Cultural Rights)*, 11 August 2000, E/C.12/2000/4 at para 43(d).

immediately.⁹⁸² For non-essential medicines, by contrast, states still have obligations, but they are to be progressively realized. General Comment 14's approach to Essential Medicines has since been affirmed by the UN CESCR on multiple occasions, and under multiple human rights instruments.⁹⁸³ This interpretation has also been widely embraced outside the UN system, including by legal scholars.⁹⁸⁴ Unsurprisingly given the drugs found on the WHO MEML, this Essential Medicines obligation has in turn been explicitly highlighted in the context of Neglected Diseases; for instance, UN Special Rapporteur on the Right to Health Paul Hunt has stated that "States parties to ICESCR may therefore be considered to have an immediate and compulsory duty to make them accessible as required by those affected by neglected diseases".⁹⁸⁵

Meanwhile, other human rights, such as the right to enjoy the benefits of scientific progress and its applications, have also been implicated in relation to access to medicines.⁹⁸⁶ While discourse around this latter right has focused largely upon access to new drugs, often implicating intellectual property, there is no reason the "benefits of science" should expire when a pharmaceutical patent does, particularly for conditions like Neglected Diseases whose treatment relies heavily on decades-old medicines. In fact, a state should have more leeway for action when

⁹⁸² For a more detailed interpretation, see UN Committee on Economic, Social and Cultural Rights (CESCR), *General Comment No. 3: The Nature of States Parties' Obligations (Art. 2, Para. 1, of the International Covenant on Economic, Social and Cultural Rights)*, 14 December 1990, E/1991/23.

⁹⁸³ See e.g., UN Committee on Economic, Social and Cultural Rights (CESCR), *General Comment No. 19: The right to social security (Art. 9 of the International Covenant on Economic, Social and Cultural Rights)*, (4 February 2008), E/C.12/GC/19 at para. 59; UN Committee on Economic, Social and Cultural Rights (CESCR), *General comment no. 22: The Right to sexual and reproductive health (article 12 of the International Covenant on Economic, Social and Cultural Rights)* (2 May 2016), E/C.12/GC/22 at para. 13.

⁹⁸⁴ As just one representative example of high-profile scholars accepting this premise, see Gruskin, Sofia & Zyde Raad. "Are Drug Companies Living Up to Their Human Rights and Responsibilities? Moving Toward Assessment" (2010) 7:9 PLoS Med e1000310, online: <<https://dx.plos.org/10.1371/journal.pmed.1000310>>.

⁹⁸⁵ Hunt, Paul, ed. *Neglected diseases: a human rights analysis*, Social, economic and behavioural (SEB) research special topics 6 (Geneva: World Health Organization, 2007).

⁹⁸⁶ See e.g., UN Committee on Economic, Social and Cultural Rights (CESCR), *General comment No. 25 (2020) on science and economic, social and cultural rights (article 15 (1) (b), (2), (3) and (4) of the International Covenant on Economic, Social and Cultural Rights)*, 30 April 2020 E/C.12/GC/25; Houston, Adam, "A Scientific Approach to Intellectual Property and Health: Innovation, Access, and a Forgotten Corner of the Universal Declaration of Human Rights" (2014) 13:4 John Marshall Review of Intellectual Property Law 794–818.

not balancing legal obligations (and political considerations) around IP. In addition, there is growing acceptance of the importance of placing Neglected Diseases within a broader human rights context, including recognition that the communities that are the most socially and economically vulnerable are frequently the most vulnerable to Neglected Diseases.⁹⁸⁷ Recognition of these broader concerns and their impact on Neglected Diseases has made its way into the practices of organizations like the WHO. Consider as an example a 2010 WHO fact sheet entitled “A human rights-based approach to neglected tropical diseases”. It highlights four national barriers characterizing NTDs: “Often hidden as they affect poor populations with little political voice; Rarely given priority in poverty reduction strategies and health sector plans; Require inter-sectoral collaboration to address underlying determinants of health; Interventions often not part of existing national health systems”.⁹⁸⁸ While this fact sheet was written with high-burden, low-resource countries in mind, these same barriers to the realization of universal human rights manifest in their own ways in low-burden, high-income states like Canada. As such, human rights can be useful tools to have in the toolbox when advocating for access to Essential Medicines. Nonetheless, this thesis does not wish to position access to off-patent Essential Medicines for Neglected Diseases as being primarily a human rights issue. There are a number of reasons for this.

First, allowing human rights to become the primary focus detracts from the other legal and normative impacts of Essential Medicines. The Essential Medicines concept is neither premised nor dependent upon human rights concepts. The formalized Essential Medicines concept of the WHO was developed outside the international human rights framework, and exerts legal influence independent of human rights claims. In fact, human rights are not referred to at all in either Mahler’s seminal 1975 report, or the inaugural WHO MEML and accompanying Expert Committee report in 1977. Nor were these foundational documents of the WHO concept of Essential Medicines developed against a backdrop of human

⁹⁸⁷ See e.g., Sun, Nina & Joseph J Amon. “Addressing Inequity: Neglected Tropical Diseases and Human Rights” (2018) 20:1 Health Hum Rights 11–25.

⁹⁸⁸ World Health Organization. *A human rights-based approach to neglected tropical diseases*, Information Sheet (2010).

rights. In the decades leading up to the WHO MEML, the WHO had adopted a staunch “‘apolitical’ medical lens untethered to human rights obligations”, which, as Meier compelling argues, led to it distancing itself from the political fray during the development of foundational human rights instruments in the early 1950s, resulting in the Organization “neglecting its UN mandate to clarify the human rights related to health”.⁹⁸⁹ One consequence of the early development of UN human rights instruments occurring separately from WHO initiatives is that while Essential Medicines have long been incorporated into human rights-driven endeavours, they have maintained a separate existence.

Some of the confusion between, and indeed conflation of, Essential Medicines and human rights may stem from the incorporation of both concepts into the landmark *Declaration of Alma-Ata* in 1978.⁹⁹⁰ *Alma-Ata*’s aspiration of “Health for All by the Year 2000” was a watershed moment for explicitly linking health and human rights, and marked a shift in the WHO’s approach to human rights issues.⁹⁹¹ However, the WHO conception of Essential Medicines both predates and is distinct from *Alma-Ata*. In fact, while *Alma-Ata* faced criticism for being more utopian than realistic, some of those critics acknowledged its inclusion of Essential Medicines as one of its practical aspects.⁹⁹² Similarly, the connections made between Essential Medicines and *Alma-Ata*’s core concept of Primary Health Care (PHC) may also have helped fuel the association of Essential Medicines with

⁹⁸⁹ Meier, Benjamin Mason, “Making Health a Human Right: The World Health Organization and the United Nations Programme on Human Rights and Scientific and Technological Developments: Making Health a Human Right” (2013) 13:2 *Journal of The Historical Society* 195–229, online: <<https://onlinelibrary.wiley.com/doi/10.1111/jhis.12017>>. This was particularly the case during the lengthy tenure (1953–1973) of Mahler’s predecessor as Director-General, Marcolino Gomes Candau. The first Director-General, Brock Chisholm (a Canadian) is generally thought to have been more receptive to human rights.

⁹⁹⁰ International Conference on Primary Health Care, “Declaration of Alma-Ata” (1978) 32:11 *WHO Chron* 428–430, notably in Art. VII(3) and Art. I, respectively.

⁹⁹¹ Rifkin, Susan B, “Alma Ata after 40 years: Primary Health Care and Health for All—from consensus to complexity” (2018) 3:Suppl 3 *BMJ Glob Health* e001188; Meier, Benjamin Mason et al., “ALMA-ATA at 40: A Milestone in the Evolution of the Right to Health and an Enduring Legacy for Human Rights in Global Health”, *Health & Human Rights Journal* (Blog), (5 September 2018), online: <<https://www.hhrjournal.org/2018/09/alma-ata-at-40-a-milestone-in-the-evolution-of-the-right-to-health-and-an-enduring-legacy-for-human-rights-in-global-health/>>.

⁹⁹² See e.g., Passmore, R. “The Declaration of Alma-Ata and the Future of Primary Care” (1979) 314:8150 *The Lancet* 1005–1008, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673679925728>>.

extremely basic care in resource-poor settings, an idea which, as discussed elsewhere in this thesis, has contributed to discouraging acceptance and adoption of the concept in HICs.⁹⁹³ This is despite the fact that in crafting the inaugural MEML, the WHO Expert Committee had explicitly highlighted the applicability of Essential Medicines to all states, while also considering, and rejecting, a much shorter primary care list of drugs for resource-poor settings.⁹⁹⁴ Thus, while Essential Medicines can be employed alongside, or integrated with, human rights concepts, it has never been the case that doing so has been necessary to endow them with influence.

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The second reason for sidelining human rights is that a human rights-focused approach is less likely to be effective in Canada than it has been elsewhere. International human rights treaties like the ICESCR do not have direct domestic application in Canada.⁹⁹⁵ Similarly, while constitutional provisions have been leveraged as a powerful force for access to Essential Medicines in other countries, Canada has not domestically enshrined a constitutional right to access to medicines (Essential or otherwise), or to health or healthcare more broadly. Certainly, no such explicit right is present in the text; as the Supreme Court of Canada noted in

Commented [AH7]: Toussaint?

⁹⁹³ See e.g., Chan, Margaret. "Return to Alma-Ata" (2008) 372:9642 *The Lancet* 865–866, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673608613720>>. It is true, however, that the stripped-to-Essentials ideas of both *Alma-Ata's* concept of Primary Health Care (PHC) and Essential Medicines share roots, such as Djukanovic, V et al., eds. *Alternative approaches to meeting basic health needs in developing countries: a joint UNICEF/WHO study* (Geneva: 1975). There is also a slight touch of irony in the fact that one person sometimes credited with introducing the term Neglected Diseases – in the slightly different form of "Great Neglected Diseases" – was Kenneth Warren; around the same time, Warren would also co-author the seminal paper on the concept of "Selective Primary Health", an even more stripped-down model that would compete for attention with PHC. Walsh, Julia A & Kenneth S Warren. "Selective Primary Health Care: An Interim Strategy for Disease Control in Developing Countries" (1979) 301:18 *N Engl J Med* 967–974, online: <<http://www.nejm.org/doi/abs/10.1056/NEJM197911013011804>>; see also Keating, Conrad, "Ken Warren and the Rockefeller Foundation's great neglected diseases network, 1978-1988: the transformation of tropical and global medicine" (2014) 20 *Suppl 1 Mol Med* S24-30.

⁹⁹⁴ WHO Expert Committee. *The selection of essential drugs*, Technical report series / World Health Organization 615 (World Health Organization, 1977) at p. 13. This distinction between Essential Medicines and medicines for primary care has also been echoed by Mahler himself. Mahler, Halfdan. "The Meaning of 'Health for All by the Year 2000'" (2016) 106:1 *American Journal of Public Health* 36–38.

⁹⁹⁵ Even as recent decisions like *Toussaint v. Canada (Attorney General)* 2022 ONSC 4747 suggest a potentially broader approach to Canada's human rights treaty obligations in future (particularly at paras. 181-182), the status quo that "[i]nternational treaties and conventions are not part of domestic law and have no domestic legal consequences unless they are implemented by statute" is also reiterated (at para. 173).

Chaoulli, the “Charter does not confer a freestanding constitutional right to health care”.⁹⁹⁶ To end any suspense, the work of attempting to shoehorn an unambiguous Charter right to Essential Medicines into Canadian law will be left to other scholars.

Nonetheless, it is worth noting the international trend towards the incorporation of health-related rights into national constitutions, including a relatively small but increasing number that explicitly address access to medicines.⁹⁹⁷ Such constitutional recognition has even been identified by the WHO as a country progress indicator.⁹⁹⁸ As such, here is another area where Canada, whose Charter of Rights and Freedoms was once a leading example of a progressive rights instrument, is falling behind. As one striking comparison, the landmark South African case on human rights and access to medicines of *Minister of Health v Treatment Action Campaign (TAC)* (2002) draws upon South Africa’s Bill of Rights, an instrument inspired in part by Canada’s Charter, but which also incorporates both an explicit right to healthcare and requires reference to international law, each of which influenced the outcome.⁹⁹⁹ It remains true that constitutional recognition of a right to health “is neither a guarantee nor an essential step”.¹⁰⁰⁰ That said, explicit inclusion of such a right, and clearer domestic recognition of international legal obligations, would nevertheless make human rights a more effective tool for ensuring access to Essential Medicines in Canada.

This leads to the third reason for putting human rights to the side, which is that overreliance on them at the expense of other tools may lead to unsatisfactory outcomes. For instance, human rights may be insufficient to address the underlying

⁹⁹⁶ *Chaoulli v. Quebec (Attorney General)*, [2005] 1 S.C.R. 791, 2005 SCC 3 at para. 105.

⁹⁹⁷ Perehudoff, Katrina S, Brigit Toebe & Hans Hogerzeil, “Essential Medicines in National Constitutions: Progress Since 2008” (2016) 18:1 Health Hum Rights 141–156.

⁹⁹⁸ Perehudoff, SK, RO Laing & HV Hogerzeil. “Access to essential medicines in national constitutions” (2010) 88:11 Bull World Health Organ 800–800, online: <<http://www.who.int/bulletin/volumes/88/11/10-078733.pdf>>.

⁹⁹⁹ *Minister of Health v Treatment Action Campaign (TAC)* (2002) 5 SA 721 (CC). Ironically, this case deviates from the General Comment 14 approach of immediate realization of core obligations (at para. 25). For further discussion of the Charter/Bill of Rights comparison in a health and human rights context, see Houston, Adam R, “The Consumption of Ideas: Tuberculosis, the Constitutions of Canada and South Africa, and the Progressive Development of Human Rights Instruments” (2018) 44:1 Queen’s Law Journal.

¹⁰⁰⁰ Perehudoff, SK, RO Laing & HV Hogerzeil. “Access to essential medicines in national constitutions” (2010) 88:11 Bull World Health Organ 800–800, online: <<http://www.who.int/bulletin/volumes/88/11/10-078733.pdf>>.

systemic issues affecting access, serving to bandage the wound without healing it. As Kaczynski highlights, numerous criticisms can be levelled at human rights as not being up to the task of ensuring access to Essential Medicines, since they are a tool geared towards minimum protections rather than overhauling systems that underpin fundamental inequalities.¹⁰⁰¹ In her view, mainstream constructions visible in human rights cases around access to medicines “see the right to health as in no deep tension with the prevailing political economy”.¹⁰⁰² This rings true in the context of access to off-patent Essential Medicines; a right to a product that isn’t actually available in the first place is of little benefit.

In any case, many of the same outcomes may be possible whether or not they are framed in human rights language. To offer an example in the Neglected Diseases context, Sun and Amon are critical of the fact that while “both the World Health Assembly resolution [on NTDs] and SDG 3 provide a strong framework for action, neither explicitly references the human right to the highest attainable standard of health or describes a rights-based approach to NTDs’ elimination”.¹⁰⁰³ Even in the absence of explicit human rights language, however, the WHA resolution mentions the need to ensure the continuous availability and affordability of Essential Medicines for NTDs, while SDG 3 makes multiple references to Essential Medicines; this underscores once again that human rights are not an inherent or integral component of Essential Medicines, even if they can complement each other in useful ways.¹⁰⁰⁴ At the same time, improved access to Essential Medicines, regardless of whether human rights principles were invoked along the way, helps to realize human rights, such as the right to health, in practice. In other words, whether or not an outcome is framed in human rights language

¹⁰⁰¹ Kaczynski, Amy. “The Right to Medicines in an Age of Neoliberalism” (2019) 10:1 *Humanity* 79–107, online: <<https://muse.jhu.edu/article/722746>>.

¹⁰⁰² Kaczynski, Amy. “The Right to Medicines in an Age of Neoliberalism” (2019) 10:1 *Humanity* 79–107, online: <<https://muse.jhu.edu/article/722746>>.

¹⁰⁰³ Sun, Nina & Joseph J Amon. “Addressing Inequity: Neglected Tropical Diseases and Human Rights” (2018) 20:1 *Health Hum Rights* 11–25.

¹⁰⁰⁴ World Health Assembly, “Neglected Tropical Diseases” (27 May 2013) WHA66.12, online: <https://www.who.int/neglected_diseases/mediacentre/WHA_66.12_Eng.pdf>; United Nations, *Transforming Our World: The 2030 Agenda for Sustainable Development*, A/RES/70/1 (New York: United Nations, 2015).

may not change the value of the outcome itself. As Hogerzeil asks, “in what sense is a rights-based programme more than just a good public health programme?”¹⁰⁰⁵

All of this said, taking the spotlight off human rights within this thesis should not be confused with dismissing them entirely. Indeed, while recognizing their limitations, the author of this thesis has oft described himself as a “human rights guy”. For one, human rights can be a useful advocacy tool in the access toolkit even without express legal force. As Tasoulas and Vayena suggest, “law is just one mechanism of implementation that exists alongside others, including social conventions, public opinion, and the instillation of a rights-respecting ethos”.¹⁰⁰⁶ After all, Canada is a country that has often tried to project an international image resting at least partly on being seen as a supporter of both global health and human rights.¹⁰⁰⁷ Thus, human rights can be employed as a moral cudgel even where they lack binding force.

Human rights standards similarly offer another metric for examining what might reasonably fall within the scope of access to Essential Medicines in Canada. Here, it should be recognized that there remains controversy about the scope of the core obligation to immediately provide Essential Medicines, as laid out in General Comment 14. Were the WHO MEML to set an inviolable minimum floor, then Canada would have immediate obligations around all the Essential Medicines raised in this thesis. However, a more appropriate reading recognizes that the Model List is intended to be a model to be adapted, not an inviolable diktat. As Perehudoff and Forman write:

Essential medicines are arguably the most precise element of the minimum core as they refer to a WHO concept that gives rise to a finite Model List of Essential Medicines. However, this precision is illusive.

¹⁰⁰⁵ Hogerzeil, Hans. “Essential medicines and human rights: what can they learn from each other?” (2006) 84:5 Bull World Health Organ 371–375, online: <<http://www.who.int/bulletin/volumes/84/5/371.pdf>>.

¹⁰⁰⁶ Tasioulas, John & Effy Vayena. “Getting human rights right in global health policy” (2015) 385:9978 Lancet e42-44.

¹⁰⁰⁷ Nixon, Stephanie A et al., “Canada’s global health role: supporting equity and global citizenship as a middle power” (2018) 391:10131 The Lancet 1736–1748, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673618303222>>.

WHO's Model List is intended to be further tailored by domestic governments to the local context of disease, infrastructure, and capital, resulting in a national list that is flexible and responsive to local contingencies.¹⁰⁰⁸

The assessment of this obligation is further complicated in the case of countries such as Canada who are legally bound by the ICESCR, but have never developed a national EML to be assessed. There is remarkably little guidance in this regard, perhaps reflecting the neglect of HICs in the Essential Medicines discourse. Maybe the clearest indicator comes in a report to the General Assembly by Special Rapporteur on the Right to Health Paul Hunt, who states: "If a State declines to prepare its own national essential medicines list, the WHO model list will apply, subject to any obvious contextual revisions".¹⁰⁰⁹ This seems a rather common-sense approach. The question nevertheless remains what those "obvious contextual revisions" are, particularly against the backdrop of aforementioned considerations like the local context of both diseases and the resources available to respond to them.

Here, the local context of disease might weigh against the inclusion of drugs for Neglected Diseases in Canada; at the same time, the fact that there are still patients who need them, disproportionately drawn from marginalized groups, might mean excluding such drugs would not be an "obvious" textual revision. Taking into consideration Canada's available resources would point in the opposite direction; while Canada might have a smaller burden of such diseases than many countries, it also has greater resources to address that smaller burden. It makes little sense to impose a human rights obligation on a high-burden country with fewer resources to provide Essential Medicines, yet permit a high-resource country

¹⁰⁰⁸ Perehudoff, Katrina & Lisa Forman. "What Constitutes 'Reasonable' State Action on Core Obligations? Considering a Right to Health Framework to Provide Essential Medicines" (2019) 11:1 *Journal of Human Rights Practice* 1–21, online: <https://academic.oup.com/jhrp/article/11/1/1/5482219>.

¹⁰⁰⁹ Hunt, Paul, *Report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health*, A/61/338 (United Nations General Assembly, 2006) at para. 57.

that could easily afford the relatively small quantity of existing, generally inexpensive drugs necessary to treat disproportionately marginalized patients not to do so. This suggests that even if Essential Medicines on the WHO MEML fall short of inclusion on a Canadian EML, they should nevertheless be available as part of Canada's broader ICESCR obligation to take steps "to the maximum of its available resources, with a view to achieving progressively the full realization of" the right to health. Indeed, the UN CESCR has underscored that even in times of severe resource constraints, "the vulnerable members of society can and indeed must be protected by the adoption of relatively low-cost targeted programmes".¹⁰¹⁰ In other words, the WHO MEML serves as a valuable reference point for what drugs should at least be formally available in Canada, even beyond the immediate access obligations of those drugs on a Canadian EML.

Similarly, the flipside of progressive realization of human rights is the principle of non-retrogression.¹⁰¹¹ Some authors have suggested that removal of a drug from a benefits scheme might be considered a prohibited retrogression of the right to health.¹⁰¹² If such an act could violate the principle of non-retrogression, what about actions contributing to the disappearance of a drug not merely from the benefits scheme but from the market entirely? What about when that drug is not merely a medicine but an Essential Medicine? Such questions arise even before the disproportionate impact on identifiable vulnerable populations is taken into account; those impacts in turn serve to raise further questions of equity and equality that may themselves more easily ground legal actions rooted in human rights in Canada.¹⁰¹³ In any case, the issue of the precise boundaries of state

¹⁰¹⁰ UN Committee on Economic, Social and Cultural Rights (CESCR), *General Comment No. 3: The Nature of States Parties' Obligations (Art. 2, Para. 1, of the International Covenant on Economic, Social and Cultural Rights)*, 14 December 1990, E/1991/23 at para.12.

¹⁰¹¹ UN Committee on Economic, Social and Cultural Rights (CESCR), *General Comment No. 3: The Nature of States Parties' Obligations (Art. 2, Para. 1, of the International Covenant on Economic, Social and Cultural Rights)*, 14 December 1990, E/1991/23 at para.9.

¹⁰¹² Khachigian, Levon M, "Pharmaceutical patents: reconciling the human right to health with the incentive to invent" (2020) 25:7 *Drug Discov Today* 1135–1141.

¹⁰¹³ See e.g., Attaran, Amir, "Take your Medicine?: The Risk of Patient-led Litigation in Canada's Medicine Access System" (2009) 3:1 *McGill Journal of Law and Health* 3–20.

obligations around Essential Medicines is an evolving one.¹⁰¹⁴ For the purposes of a thesis intentionally spotlighting other issues, suffice to say that Canada is clearly not doing all it can, to the maximum of available resources, to ensure that off-patent Essential Medicines for Neglected Diseases are available to the small number of disproportionately vulnerable people who need them.

Finally, there are also practical lessons to be drawn from the experiences of other countries where human rights at the international and national levels have been central to improving access to drugs (both Essential Medicines and otherwise). One such lesson is that having an explicit list of medicines such as an EML helps to temper a broader right of access to medicines. Some rather bold predictions have been made of the consequences should current international human rights standards on access to medicines be applied in Canada.¹⁰¹⁵ Nevertheless, in countries where a broader right of access to medicines has been readily litigable, realization of that right has raised complications ranging from budgetary constraints to the need to balance litigation of individual claims against systemic reform that might address the same concerns more effectively.¹⁰¹⁶ By contrast, clear reference to an Essential Medicines list can help to mitigate these

¹⁰¹⁴ UN Economic and Social Council. *An Evaluation of the Obligation to Take Steps to the "Maximum of Available Resources" under an Optional Protocol to the Covenant*. E/C.12/2007/1 (United Nations, 2007). It should be acknowledged that some of these emerging norms are built upon an optional protocol to which Canada is not a party, further diluting its direct legal applicability. Forman, Lisa. "Can Minimum Core Obligations Survive a Reasonableness Standard of Review Under the Optional Protocol to the International Covenant on Economic, Social and Cultural Rights?" (2016) 47:2 *Ottawa Law Review*. See also Zinzombe, Shamiso, "Harnessing the Human Rights Reasonableness Principle for Access to Medicine" (2015) 3:2 *Groningen Journal of International Law* 1–16.

¹⁰¹⁵ For instance, Burningham suggests recognition of international human rights standards would take Canada well beyond standard-of-care drugs on the WHO MEML, extending to "experimental therapies that, while unproven, are reasonably anticipated by patients to have some positive effects" on the grounds of Canadian courts taking into account the "emotional responses" linked to "the stress, disappointment and feelings of hopelessness associated with denial of funding for treatment". Burningham, Sarah. *Courts, Challenges, and Cures: Legal Avenues for Patients with Rare Diseases to Challenge Health Care Coverage Decisions*, (2015) 1-1 *Canadian Journal of Comparative and Contemporary Law* 317, online: <<http://www.canlii.org/t/6vr>> at p.341-342.

¹⁰¹⁶ Brazil and Colombia are often referenced in this context. For an insightful discussion of these issues in Colombia, see Arrieta-Gómez, Aquiles Ignacio, "Realizing the Fundamental Right to Health through Litigation: The Colombian Case" (2018) 20:1 *Health Hum Rights* 133–145. For a sample of Brazilian explorations of these issues see e.g., Biehl, João et al., "Between the court and the clinic: lawsuits for medicines and the right to health in Brazil" (2012) 14:1 *Health Hum Rights* E36-52; Chieffi, Ana Luiza, Rita De Cassia Barata Barradas & Moisés Golbaum, "Legal access to medications: a threat to Brazil's public health system?" (2017) 17:1 *BMC Health Serv Res* 499, online: <<http://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-017-2430-x>>.

concerns. For instance, one study early in the wake of General Comment 14 examined 71 court cases from 12 countries.¹⁰¹⁷ Of particular note, while the majority of cases were successful, the study also found that most negative rulings “were based on a recognition of the limitations specified in the national essential medicines list”; in a quarter of the unsuccessful cases examined, “the court upheld the national essential medicines list and ruled that there was no medical need for the requested medicine for this patient”.¹⁰¹⁸ Indeed, the authors of the study emphasize the importance of Essential Medicines as a tool for delineating the boundaries of state obligations around the right to health, and explicitly conclude that “constitutional guarantees on access to health care services should be well defined, for example through reference to a national list of essential medicines, to prevent abuse”.¹⁰¹⁹ The lesson to be drawn here isn’t one inexorably rooted in human rights, however; it is that a Canadian EML, and other lists like a Canadian formulary, could help manage legal entitlements, however those entitlements are framed.

This interlude illustrates that human rights are a high-profile tool that is complementary, but not integral, to the question of access to off-patent Essential Medicines for Neglected Diseases. Canada does have obligations with respect to the right to health, and a range of other human rights with implications for access to these drugs, under international law. Developing a domestic Canadian Essential Medicines List with reference to the WHO MEML would aid in fulfilling those obligations, while also helping to define their precise parameters within Canada. At the same time, lists of important drugs such as a Canadian EML and the WHO MEML would serve as useful points of reference even in the absence of any overt reference to human rights. As such, while the human rights aspects of Essential

¹⁰¹⁷ Hogerzeil, Hans V et al. “Is access to essential medicines as part of the fulfilment of the right to health enforceable through the courts?” (2006) 368:9532 *The Lancet* 305–311, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673606690764>>.

¹⁰¹⁸ Hogerzeil, Hans V et al. “Is access to essential medicines as part of the fulfilment of the right to health enforceable through the courts?” (2006) 368:9532 *The Lancet* 305–311, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673606690764>>.

¹⁰¹⁹ Hogerzeil, Hans V et al. “Is access to essential medicines as part of the fulfilment of the right to health enforceable through the courts?” (2006) 368:9532 *The Lancet* 305–311, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673606690764>>.

Medicines should not be forgotten, and indeed are useful additions to the advocacy toolbox, they ultimately serve to reinforce the points made throughout this thesis in other ways, rather than introduce a completely novel tool indispensable for bringing Essential Medicines within the legal fold. This being the case, while the discussion of Essential Medicines will continue, the overt discussion of human rights will be left in this section.

Chapter 9: Essential Medicines in Canada

Essential Medicines and pharmacare

Having recognized the importance of access to off-patent Essential Medicines for Neglected Diseases in Canada – and the broader implications for medicines both at home and abroad – the issue now becomes one of what to do about it. A basic first step is to identify drugs necessary for patient care. As will be discussed, this process involves not only examination of which medicines are most important for healthcare in Canada, but which medicines are not formally available at all. Explicitly identifying and categorizing medicines – listing them – is a fundamental step in all instances. This information will be useful for interventions to improve access to treatment of Neglected Diseases; however, it will also have far wider implications for pharmaceutical policy in Canada. This includes the long-held aspiration of many healthcare pundits: Pharmacare.

After all, despite the hallowed status of universal healthcare in the pantheon of Canadian self-mythology, the harsh reality is that Canadian Medicare does not include pharmacare.¹⁰²⁰ This has long made it an anomaly among high-income states offering universal healthcare.¹⁰²¹ Furthermore, its outlier status is no longer strictly among HICs; Canada has also become increasingly out of step normatively at the global level in the wake of a renewed global push for universal health coverage, exemplified by its inclusion in the UN's Sustainable Development Goals. Here, pharmacare and Essential Medicines intersect directly: SDG 3.8 is to “Achieve universal health coverage, including financial risk protection, access to quality essential health-care services, and access to safe, effective, quality and affordable essential medicines and vaccines for all”.¹⁰²² As yet, direct Canadian engagement with SDG 3.8 has not been promising. It is included on the Government

¹⁰²⁰ Nor, among other issues, dental care or eye care, though these other gaps are beyond the scope of this thesis.

¹⁰²¹ See e.g., Brandt, Jaden, Brenna Shearer & Steven G Morgan, “Prescription drug coverage in Canada: a review of the economic, policy and political considerations for universal pharmacare” (2018) 11 J Pharm Policy Pract 28. These parameters of course exclude the United States, Canada's traditional frame of reference for feeling superior about universal healthcare.

¹⁰²² United Nations, *Transforming Our World: The 2030 Agenda for Sustainable Development*, by United Nations, A/RES/70/1 (New York: United Nations, 2015).

of Canada's website tracking Canada's progress on the SDGs. However, while the metrics for assessing many of the SDGs are listed, as of this writing (nearly halfway to the SDG deadline of 2030), Statistics Canada is still "exploring data sources" for this particular goal.¹⁰²³ This is perhaps symbolic of where Canada finds itself in the international conversation: not in its desired, and sometimes presumed, position as a global health leader, but instead somewhere further back in the pack. The blunt fact is that Canada currently has no way to formally assess access to "safe, effective, quality and affordable essential medicines" because it has no formal reference point for what medicines are essential in Canada. If the metric is the WHO MEML, Canada clearly falls short, as detailed thus far (See **Table 1**). At the same time, Canada also lacks a tailored domestic alternative. Thus, one immediate benefit to adopting a Canadian EML or explicitly engaging with the WHO MEML would be that it would provide a reference point for evaluating Canada's progress on achieving shared international goals such as the SDGs.

Doing so would also play a valuable role at home, providing an anchor point for ensuring access to medicines, or at least particularly important ones. This is already recognized, implicitly and increasingly explicitly; references to "essential medicines" have long infiltrated the Canadian pharmacare conversation. However, the term itself has seldom been clearly defined in a Canadian context, with its usage remaining intuitive yet vague rather than denoting a formalized set of medicines.¹⁰²⁴ At the conceptual level, of course, some overlap between pharmacare and Essential Medicines has always been present. As noted earlier, the "universal" in universal pharmacare refers to all people having access to drug

¹⁰²³ Government of Canada, "Goal 3 – Good health and well-being", Sustainable Development Goals Data Hub, online: <<https://www144.statcan.gc.ca/sdg-odd/goal-objectif03-eng.htm>>. Accessed 10 April 2022.

¹⁰²⁴ For examples, see e.g., Lewis, Steven, "It Won't Be Easy: How to Make Universal Pharmacare Work in Canada" (2020) 9:1 *Int J Health Policy Manag* 1–5; Morgan, Steven G & Katherine Boothe, "Universal prescription drug coverage in Canada: Long-promised yet undelivered" (2016) 29:6 *Healthc Manage Forum* 247–254, online: <<http://journals.sagepub.com/doi/10.1177/0840470416658907>>; Salehi, Leila, "National pharmacare: Time to move forward" (2016) 62:7 *Can Fam Physician* 544–546.

coverage, not to an infinite formulary comprising every drug in the universe.¹⁰²⁵ As such, a feasible pharmacare program necessitates deciding which drugs are more and less essential.

To be clear: pharmacare itself is no panacea for the issues that find certain Essential Medicines outside of formal access channels in the first place. It could not be counted an unabashed success if Canada's dream of pharmacare were realized for many drugs going well beyond the scope of the WHO MEML, while access to globally recognized Essential Medicines that serve as the standard of care in Canada remained in a precarious legal grey area. Indeed, even as pharmacare might help alleviate longstanding woes in Canada's health system, it potentially risks further sidelining ongoing concerns around accessing off-patent Essential Medicines for Neglected Diseases. This is all the more likely in the absence of an explicit point of reference for identifying the Essential Medicines that are absent from the market even as they form the standard of care. Avoiding this outcome is a further reason why Essential Medicines need to be part of the pharmacare discussion. As Essential Medicines and pharmacare draw closer together at both the international and domestic levels, there are opportunities to reconcile these issues.

Why doesn't Canada have pharmacare?

So why does Canada lack universal pharmacare, unlike other high-income countries with universal healthcare systems? This thesis, lengthy though it is, is not going to devolve into a treatise on this broader question, let alone Medicare as a whole. However, a brief exploration of the history of pharmacare in Canada both illustrates why Canada lacks what true universal healthcare demands, and the role of Essential Medicines in offering a remedy. In the mythologized Coles Notes version, Canada's universal healthcare system was the brainchild of Tommy Douglas, who initiated a similar program at the provincial level as Premier of Saskatchewan (1944-1961), and subsequently brought the idea to Ottawa as the

¹⁰²⁵ For clarity, "universal" also does not necessarily imply single payer, although that does sometimes seem to be assumed by at least some parties in the Canadian context. This issue of single vs. multipayer pharmacare is outside the scope of this thesis.

first federal leader (1961-1971) of the newly re-christened New Democratic Party (NDP).¹⁰²⁶ The reality is of course a bit more complex than a one-man show.¹⁰²⁷ The emergence of Medicare was also reflective of international trends at the time, as Canada was one of many Western democracies moving towards universal healthcare in the post-war period. By 1957, the *Hospital Insurance and Diagnostic Services Act* introduced a 50% federal contribution for certain services, including drugs provided to inpatients.¹⁰²⁸ One major difference from other countries, however, including other comparable Commonwealth countries like the United Kingdom and Australia, is that Canada did not incorporate universal pharmacare into Medicare from the beginning.¹⁰²⁹ Instead, Medicare was initiated in a stepwise fashion, with the presumption that pharmacare would be incorporated further down the road. This final step was never taken. Thus, as Lewis somewhat floridly puts it, “Pharmacare is medicare’s Achilles heel and unfinished business, Canada’s *Sagrada Familia* cathedral, its cornerstone laid in Barcelona in 1882 and still undone”.¹⁰³⁰

Pharmacare had in fact been included in the blueprints. The famed Royal Commission on Health Care (popularly known as the Hall Commission, after its chair, Emmett Hall, subsequently a justice of the Supreme Court of Canada), whose recommendations helped drive the process of Medicare at the national level, concluded that drugs prescribed by licensed health practitioners should be covered.¹⁰³¹ In doing so, it explicitly refers to “the necessity for solutions that

¹⁰²⁶ See e.g., the landmark *Saskatchewan Hospitalization Act*, 1946 SS 1946, c 82.

¹⁰²⁷ An excellent source, but also cited in tribute to a cool guy who never got to read the final draft of this thesis. RIP, Grandpa. Houston, C Stuart & W A Waiser, *Tommy’s team: the people behind the Douglas years* (Markham, ON: Fifth House, 2010).

¹⁰²⁸ Turner, J G, “The Hospital Insurance and Diagnostic Services Act: its impact on hospital administration” (1958) 78:10 Can Med Assoc J 768–770.

¹⁰²⁹ Indeed, Boothe argues that Canada considered but rejected a model of health insurance encompassing pharmacare as far back as 1945. Boothe, Katherine, “Pharmaceutical policy reform in Canada: lessons from history” (2018) 13:3–4 Health Econ Policy Law 299–322.

¹⁰³⁰ Lewis, Steven, “It Won’t Be Easy: How to Make Universal Pharmacare Work in Canada” (2020) 9:1 Int J Health Policy Manag 1–5.

¹⁰³¹ Hall, Emmett M (Chair), *Royal Commission on Health Services* (Ottawa: Queen’s Printer, 1964).P.40

enable essential drugs to be readily available and at reasonable cost”.¹⁰³² The term “essential drugs” is not defined, but from context clearly reflects drugs of particular medical importance rather than all possible drugs. To identify such drugs, the Hall Commission recommended that “the Food and Drug Directorate, with the assistance of the Advisory Committee, prepare and issue a National Drug Formulary which would be maintained on a current basis”.¹⁰³³ This National Drug Formulary “would include only those drugs which meet the specifications of the Directorate, and would be identified as such, and therefore eligible for inclusion in the Prescription Drug Benefit”.¹⁰³⁴ To this end, noting that the “necessity for legal standards to define the specifications, establish the purity and regulate the strength of drugs is recognized by a number of countries” it also discusses existing foreign reference points and their pre-existing recognition within the schedules of the *Food and Drugs Act* as official compendia of drugs, including the WHO’s *International Pharmacopoeia*.¹⁰³⁵ Presciently, the Hall Report also takes the further step of highlighting the need for the government to step in where the private manufacture and distribution of drugs does not sufficiently serve the public interest:

Although we accept that the manufacture and distribution of drugs in this country is a private enterprise venture, we have no hesitation in stating that the public interest is dominant. When we speak of the availability of a large number of specific drugs, we are talking in terms of lives and the health of people. Either the industry will itself make these drugs available at the lowest possible cost, or it will be necessary for agencies and devices of government to do so. We must not confuse

¹⁰³² Hall, Emmett M (Chair), *Royal Commission on Health Services* (Ottawa: Queen’s Printer, 1964).P.40

¹⁰³³ Hall, Emmett M (Chair), *Royal Commission on Health Services* (Ottawa: Queen’s Printer, 1964).Recommendation No.62, p.42,

¹⁰³⁴ Hall, Emmett M (Chair), *Royal Commission on Health Services* (Ottawa: Queen’s Printer, 1964).Recommendation No.62, p.42,

¹⁰³⁵ Hall, Emmett M (Chair), *Royal Commission on Health Services* (Ottawa: Queen’s Printer, 1964). Recommendation No.62 p.372-373. It highlights formal Canadian recognition of the British Pharmacopoeia and British Pharmaceutical Codex, the United States Pharmacopoeia and National Formulary, the International Pharmacopoeia, and the Codex Français.

the distribution of essential drugs with the distribution of cosmetics and sundries.¹⁰³⁶

Thus, from the beginning, a government role in ensuring affordable access to a list of vital medicines was not only contemplated, but involved a more active role than simply cutting cheques to the provinces. In practice, however, a gradual approach was adopted when putting the Hall Commission's recommendations into action via the *Medical Care Act* in 1966. Some have argued this stepwise approach seemed sensible at the time:

There was some logic to this sequencing. First, hospital and medical care were far more important components of healthcare and related costs at the time. If resource constraints, federal-provincial politics and operational pragmatism required that health insurance be built in stages, hospital and medical care were the stages to begin with.¹⁰³⁷

The same authors suggest this approach may have been influenced by the rapidly evolving nature of pharmaceuticals since WWII, including patterns of usage and their increasing (though perhaps low by today's standards) costs; under such circumstances, Morgan and Daw argue policy makers were waiting for pharmaceutical spending to plateau before expanding Medicare to include pharmacare.¹⁰³⁸ Boothe, meanwhile, makes the intriguing argument that while politicians of the era who held similar views, particularly on the affordability of pharmacare, ultimately held sufficient sway in the corridors of power to keep it from being implemented, their underlying views on affordability at the time were

¹⁰³⁶ Hall, Emmett M (Chair), *Royal Commission on Health Services* (Ottawa: Queen's Printer, 1964) Recommendation No.62, p.42.

¹⁰³⁷ Morgan, Steven G & Jamie R Daw, "Canadian pharmacare: looking back, looking forward" (2012) 8:1 Healthc Policy 14–23. (citations omitted).

¹⁰³⁸ Morgan, Steven G & Jamie R Daw, "Canadian pharmacare: looking back, looking forward" (2012) 8:1 Healthc Policy 14–23.

in fact inaccurate in the first place.¹⁰³⁹ Whatever the case, this final step of incorporating drug coverage was not taken. Subsequently, a 1971 proposal was prepared, again including the institution of a national formulary, but does not seem to have made it far outside of Pierre Trudeau's cabinet.¹⁰⁴⁰ This would prove to be the last time pharmacare would achieve a high federal profile for over a quarter century.

Stepping in to fill the void during the intervening decades, individual provinces adopted their own less-than-universal pharmacare programs. These were sometimes designed less as an extension of Medicare than as a safety net for certain vulnerable groups; indeed, some provinces administered their drug programs as not so much health programs as welfare programs.¹⁰⁴¹ This highlights once more the intersection of access to medicines and the particular needs of vulnerable communities. In practice, this provincial patchwork led to inequities across the country going beyond differences in the drugs receiving coverage; for instance, some provinces established their programs based primarily upon age, and others primarily upon income.¹⁰⁴² The particular drugs covered varied between provinces as well, an issue that, as noted earlier, persists today. A 2017 study by the PMPRB found about 79% agreement across the country for a subset of commonly used drugs.¹⁰⁴³ Agreement for single-source drugs was even lower, at an average of 67%.¹⁰⁴⁴

¹⁰³⁹ Boothe, Katherine, "Pharmaceutical policy reform in Canada: lessons from history" (2018) 13:3-4 Health Econ Policy Law 299-322.

¹⁰⁴⁰ Boothe, Katherine, *Pharmaceutical Programs and Social Policy Development: Comparing Canada, Australia and the UK* University of British Columbia, (2010) at p.64-65.

¹⁰⁴¹ Morgan, Steven G & Jamie R Daw, "Canadian pharmacare: looking back, looking forward" (2012) 8:1 Healthc Policy 14-23.

¹⁰⁴² See e.g., Busby, Colin, Jonathan Pedde *Should public drug plans be based on age or income?* (2015) CD Howe Institute, online: <https://www.cdhowe.org/sites/default/files/attachments/research_papers/mixed/Commentary_417.pdf>.

¹⁰⁴³ Patented Medicine Prices Review Board, *Alignment among public formularies in Canada, part 1* (2017), online: <<http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1327>>. Other studies have found similar differences between provincial formularies, for instance in the inclusion of new drugs. See e.g., Grégoire, J P et al., "Inter-provincial variation in government drug formularies" (2001) 92:4 Can J Public Health 307-312.

¹⁰⁴⁴ Patented Medicine Prices Review Board, *Alignment among public formularies in Canada, part 1* (2017), online: <<http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1327>>.

While provinces took coverage of some medicines for certain populations into their own hands, federal energies around pharmaceuticals in the wake of the enactment of Medicare were redirected towards patented products, a simpler target within the clear jurisdiction of the federal government. As Boothe frames it:

[Such reforms] required limited outlay of federal resources, could be enacted without consultation with provincial governments, and although they required confrontation with one major organized interest, the pharmaceutical industry, this actor enjoyed far less influence and prestige than the Canadian Medical Association, or industry groups in other countries.¹⁰⁴⁵

Thus, the broader issue of universal pharmacare became sidetracked by interventions rooted in intellectual property. The resulting reforms to the *Patent Act* in the late 1960s permitted the widespread grant of compulsory licences for pharmaceutical products.¹⁰⁴⁶ Compulsory licences for domestic manufacture had been permitted since the 1920s, but the reforms expanded the scope of compulsory licensing to permit importation (itself a recommendation of the Hall Commission).¹⁰⁴⁷ By one count, a total of 613 such licences were granted to import or manufacture patented medicines between 1969 and 1992.¹⁰⁴⁸ This generous granting of compulsory licences for pharmaceutical products helped Canada to develop a thriving generic pharmaceutical industry, including major companies like Apotex and Novopharm.¹⁰⁴⁹ The availability of compulsorily licenced generics also

¹⁰⁴⁵ Boothe, Katherine, *Pharmaceutical Programs and Social Policy Development: Comparing Canada, Australia and the UK* University of British Columbia, (2010) at p.63.

¹⁰⁴⁶ By way of exceedingly brief explanation, a compulsory licence overrides the monopoly element of a patent; the patent remains valid, and the patent-holder receives remuneration, but they lose control over who will be granted a licence to use the patent (i.e., the licence becomes compulsory).

¹⁰⁴⁷ *Hall Commission*, Recommendation No.67, p.42.

¹⁰⁴⁸ Reichman, Jerome H & Catherine Hasenzahl. *Non-voluntary Licensing of Patented Inventions: Historical Perspective, Legal Framework under TRIPS, and an Overview of the Practice in Canada and the USA*, Issue Paper No. 5 (ICTSD UNCTAD, 2003).

¹⁰⁴⁹ Reichman, Jerome H & Catherine Hasenzahl. *Non-voluntary Licensing of Patented Inventions: Historical Perspective, Legal Framework under TRIPS, and an Overview of the Practice in Canada and*

helped keep the cost of pharmaceuticals down, even as many patients continued to pay out of pocket, thus letting off steam while pharmacare sat on the backburner.

In turn, drugs administered outside a hospital setting remained excluded from classification as “medically necessary services” when the *Canada Health Act* was enacted in 1984.¹⁰⁵⁰ Salehi’s assertion that the omission of broader access to medicines during these reforms was because of “their marginal role in health care and health care delivery at the time of the *Canada Health Act*’s enactment” is perhaps dependent on the precise boundaries of what one terms “marginal”.¹⁰⁵¹ Nonetheless, particularly under the compulsory licencing regime up until that point, they were likely less of a financial concern than would have otherwise been the case. However, other changes to Canadian pharmaceutical policy would swiftly follow, shifting this balance. A series of reforms in the mid-1980s and early 1990s, tied both to efforts to expand a research-driven pharmaceutical industry in Canada, and to trade negotiations with both the United States (ultimately resulting in the North American Free Trade Agreement, NAFTA) and the nascent World Trade Organization, led to the strengthening of patent protections for pharmaceuticals in Canada, including the elimination of matter-of-course compulsory licencing of pharmaceuticals.¹⁰⁵² These reforms also led to the creation of the Patented Medicine Prices Review Board, discussed elsewhere, as a means to counterbalance the newly-strengthened monopoly powers of pharmaceutical patent holders.¹⁰⁵³

By the mid-1990s, however, around the time that the emergence of the first highly effective, but also highly priced, antiretroviral therapies for HIV helped draw attention to pharmaceutical patents and accompanying monopoly pricing as a key

the USA, Issue Paper No. 5 (ICTSD UNCTAD, 2003). Fittingly, given the history of mergers and name changes in this thesis, Novopharm is now Teva Canada.

¹⁰⁵⁰ *Canada Health Act* (R.S.C., 1985, c. C-6). It is worth reiterating that the term “medically necessary” is never defined in the Act.

¹⁰⁵¹ Salehi, Leila, “National pharmacare: Time to move forward” (2016) 62:7 *Can Fam Physician* 544–546.

¹⁰⁵² See e.g., Lexchin, Joel, “Pharmaceuticals, Patents, and Politics: Canada and Bill C-22” (1993) 23:1 *Int J Health Serv* 147–160, online: <<http://journals.sagepub.com/doi/10.2190/UCWG-YBR3-X3L0-NWYT>>; Pazderka, Bohumír, “Patent Protection and Pharmaceutical R&D Spending in Canada” (1999) 25:1 *Canadian Public Policy / Analyse de Politiques* 29, online: <<https://www.jstor.org/stable/3551400?origin=crossref>>.

¹⁰⁵³ An Act to Amend the Patent Act (R.S., 1985, c. 33 (3rd Supp.)).

access to medicines concern on the global stage, universal pharmacare once again landed on the Canadian policy agenda. The federal government's National Forum on Health report in 1998 recommended the implementation of drug coverage.¹⁰⁵⁴ In doing so, it not only acknowledged the shortcomings of the *Canada Health Act*, but the problem with treating medicines like ordinary consumer goods:

That drugs are as much a part of "medically necessary" care as are the services of physicians and of hospitals, seems now too obvious to deserve discussion. But this raises an issue that runs deeper than questions of access, appropriateness, and equity. In a fundamental sense, it implies that we do not wish to treat drugs as a "commodity", on a par with shoes and ships and sealing wax, and that it is irrational and inconsistent with our broader objectives to do so.¹⁰⁵⁵

The references to "medically necessary" drugs draw immediate links to drugs accessed under the *Canada Health Act*, while expanding the scope of how and where the term might be applied. As discussed earlier, it is not a great leap from medically necessary to Essential Medicines and indeed, the National Forum's report refers to "access to essential pharmaceuticals" while referring more than once to "drugs as an essential public good", even if it never invokes the WHO MEML or delves deeply into precisely how it might define either "medically necessary" drugs or "essential" medicines.¹⁰⁵⁶

¹⁰⁵⁴ It is interesting, however, that the term "pharmacare" never actually appears in this document. Government of Canada. "Directions for a Pharmaceutical Policy in Canada." (1998) Canada Health Action: Building on the Legacy. Synthesis Reports and Issues Papers, Volume II. Ottawa: National Forum on Health online <<https://www.canada.ca/en/health-canada/services/health-care-system/reports-publications/health-care-renewal/canada-health-action-building-legacy-volume2.html>>.

¹⁰⁵⁵ Government of Canada, "Directions for a Pharmaceutical Policy in Canada." (1998) Canada Health Action: Building on the Legacy. Synthesis Reports and Issues Papers, Volume II. Ottawa: National Forum on Health online <<https://www.canada.ca/en/health-canada/services/health-care-system/reports-publications/health-care-renewal/canada-health-action-building-legacy-volume2.html>>.

¹⁰⁵⁶ Government of Canada, "Directions for a Pharmaceutical Policy in Canada." (1998) Canada Health Action: Building on the Legacy. Synthesis Reports and Issues Papers, Volume II. Ottawa: National Forum on Health online <<https://www.canada.ca/en/health-canada/services/health-care-system/reports-publications/health-care-renewal/canada-health-action-building-legacy-volume2.html>>.

The resurgence of the idea of pharmacare continued a few years later with further recommendations for drug coverage in the 2002 report by the Commission on the Future of Health Care in Canada, “Buildings on values: the future of health care in Canada”, popularly known as the “Romanow Report” (after its chair, Roy Romanow, former Premier of Saskatchewan).¹⁰⁵⁷ This report advocates for the gradual integration of prescription drugs into the continuum of care, in a way that “will raise the floor for prescription drug coverage across Canada and lay the groundwork for the ultimate objective of bringing prescription drugs under the Canada Health Act”.¹⁰⁵⁸ In doing so, it advocates for a national formulary that will “provide consistent coverage, objective assessments, and help contain costs”.¹⁰⁵⁹ Like the National Forum, it often refers to drugs as “medically necessary”, while similarly employing the term “essential medications” (while leaving it similarly undefined).¹⁰⁶⁰ Ultimately, neither report was ultimately enough to catalyze the implementation of national pharmacare, but both helped raise its profile once more. From here, the role of Essential Medicines in this conversation would continue to grow.

The Hoskins Report and Essential Medicines

After laying fallow for close to a decade under Stephen Harper’s Conservatives, the idea of pharmacare appeared to pick up steam again some years into Justin Trudeau’s Liberal government. In the interim, private initiatives like the 2016

system/reports-publications/health-care-renewal/canada-health-action-building-legacy-volume2.html>. Interestingly, in another report, the National Forum on Health had also examined the issue of defining “medically necessary”. Despite acknowledging challenges arising from the lack of definition, the report also raises concerns about defining the term, ultimately resisting a fixed list of medically necessary services or a firm definition. Government of Canada, “Striking a Balance Working Group Synthesis Report.” (1998) Canada Health Action: Building on the Legacy. Synthesis Reports and Issues Papers, Volume II. Ottawa: National Forum on Health online <<https://www.canada.ca/en/health-canada/services/health-care-system/reports-publications/health-care-renewal/canada-health-action-building-legacy-volume2.html>>.

¹⁰⁵⁷ Romanow, Roy J (Chair), *Buildings on values: the future of health care in Canada : final report* (Saskatoon: Commission on the Future of Health Care in Canada, 2002).

¹⁰⁵⁸ Romanow, Roy J (Chair), *Buildings on values: the future of health care in Canada : final report* (Saskatoon: Commission on the Future of Health Care in Canada, 2002) at p.190.

¹⁰⁵⁹ Romanow, Roy J (Chair), *Buildings on values: the future of health care in Canada : final report* (Saskatoon: Commission on the Future of Health Care in Canada, 2002) at p.191.

¹⁰⁶⁰ Romanow, Roy J (Chair), *Buildings on values: the future of health care in Canada : final report* (Saskatoon: Commission on the Future of Health Care in Canada, 2002) at p.207.

Citizens' Reference Panel on Pharmacare in Canada had also called upon the federal government to “immediately implement universal public coverage of a minimal list of essential medications across the country” as part of a move towards pharmacare.¹⁰⁶¹ However, a crucial step towards the more formal integration of Essential Medicines into pharmacare was the establishment of the Advisory Council on the Implementation of National Pharmacare in the 2018 federal budget.¹⁰⁶² The Advisory Council’s mandate, established by Order in Council, was to “provide independent advice to the Minister of Health and the Minister of Finance on how to best implement national pharmacare in a manner that is affordable for Canadians and their families, employers and governments”.¹⁰⁶³ To aid in this process, the Advisory Council released the “Towards Implementation of National Pharmacare Discussion Paper” in June of that year.¹⁰⁶⁴ It put forward a range of options for pharmacare, including one focused not merely on Essential Medicines but the WHO MEML.

One approach could be to focus on essential medicines, particularly those used in primary health care. The World Health Organization (WHO) defines essential medicines—a few hundred in total—as those that meet the priority health care needs of the population and should be available within the context of functioning health systems at all times in adequate amounts and at a price the individual and the community can afford. Individual public and private plans could top-up this list of drugs with additional medication that would be made

¹⁰⁶¹ Citizens’ Reference Panel on Pharmacare in Canada, “Necessary Medicines: Recommendations of the Citizens’ Reference Panel on Pharmacare in Canada.” (2016) (Vancouver: Pharmaceutical Policy Research Collaboration, University of British Columbia).

¹⁰⁶² Advisory Council on the Implementation of National Pharmacare, *Towards Implementation of National Pharmacare Discussion Paper*, Discussion Paper, by Advisory Council on the Implementation of National Pharmacare, Discussion Paper (2018) at p.1.

¹⁰⁶³ Governor General of Canada, Order in Council [Advisory Council on the Implementation of National Pharmacare] (27 February 2018), online: <<https://orders-in-council.canada.ca/attachment.php?attach=35848&lang=en>>.

¹⁰⁶⁴ Advisory Council on the Implementation of National Pharmacare, *Towards Implementation of National Pharmacare Discussion Paper*, Discussion Paper, by Advisory Council on the Implementation of National Pharmacare, Discussion Paper (2018).

available to their residents or clients. This approach would ensure that all Canadians have access to a basic set of medicines, but would not cover the full complement of drugs normally used in our health care system. It would also not address the challenges of newer, high cost drugs.¹⁰⁶⁵

As detailed above, references to the (undefined) concept of Essential Medicines had appeared in pharmacare reports as far back as the Hall Commission, as well as the National Forum and the Romanow Report, and in various scholarly articles in between. However, the Advisory Council's explicit reference to the WHO MEML in the context of Canadian pharmacare counts as an important step. That said, the Advisory Council does not fully situate the WHO MEML in the Canadian context; while it indicates that not all drugs in use in Canada would be covered by pharmacare, it never acknowledges the issue of drugs on the WHO MEML not being formally available in Canada at all. This suggests once again the influence of the unspoken assumption that Canada already has access to WHO-listed Essential Medicines. In reality, premising pharmacare upon the WHO MEML would actually require the market entry of a considerable number of drugs, including more than thirty Essential Medicines for Neglected Diseases alone (see **Table 2**).

The Advisory Council contrasts this WHO MEML-based Essential Medicines approach with the option of focusing on “the most frequently prescribed drugs across a broad range of common medical conditions (e.g., diabetes, high blood pressure, etc.)”, which it suggests would “ensure all Canadians have similar access to the drugs commonly prescribed in family practice, but again... would not address the challenges of higher cost prescription drugs”.¹⁰⁶⁶ In doing so, it tacitly indicates that Essential and widely used are not synonymous, while also leaving out less commonly used, higher-cost drugs. The Advisory Council also puts forward a third

¹⁰⁶⁵ Advisory Council on the Implementation of National Pharmacare, *Towards Implementation of National Pharmacare Discussion Paper*, Discussion Paper, by Advisory Council on the Implementation of National Pharmacare, Discussion Paper (2018) at p.12.

¹⁰⁶⁶ Advisory Council on the Implementation of National Pharmacare, *Towards Implementation of National Pharmacare Discussion Paper*, Discussion Paper, by Advisory Council on the Implementation of National Pharmacare, Discussion Paper (2018) at p.12.

“more comprehensive approach [that] could be taken by providing coverage for a larger list of drugs equivalent to what some of the more generous provincial formularies currently provide (although not an open formulary where all drugs approved for sale are included)”.¹⁰⁶⁷ In response to the Advisory Council’s discussion paper, the invocation of Essential Medicines received support from various parties, including the Canadian Medical Association (CMA), who in their submission recommended the Council engage “with the federal and provincial/territorial governments and the health insurance industry on the feasibility of a universal federally funded ‘essential medicines’ prescription drug plan as a scalable approach to the implementation of a national pharmacare plan”.¹⁰⁶⁸ This would foreshadow what was to come.

The next major step would be the landmark 2019 report introduced early in this thesis. That report, formally titled “A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare,” is more popularly known as the “Hoskins Report” (after its chair, Eric Hoskins, the former Minister of Health and Long-Term Care for Ontario).¹⁰⁶⁹ The Hoskins Report follows the lead of the Council’s discussion paper in explicitly incorporating both the concept of Essential Medicines and the WHO MEML, but utilizes them somewhat differently. In the event, the Hoskins Report does not settle on one of the three options presented in the discussion paper, but draws together aspects of all three. As such, it does not simply adopt or adapt the WHO MEML. Rather, it differentiates between the Essential Medicines concept and the contents of the WHO MEML itself, while integrating both into the Report. It also continues the trend, evinced in the discussion paper, of shifting away from describing drugs as “medically necessary” – language linked to the *Canada Health*

¹⁰⁶⁷ Advisory Council on the Implementation of National Pharmacare, *Towards Implementation of National Pharmacare Discussion Paper*, Discussion Paper, by Advisory Council on the Implementation of National Pharmacare, Discussion Paper (2018) at p.12.

¹⁰⁶⁸ Canadian Medical Association, *CMA submission: Implementation of National Pharmacare*, Submission to the Advisory Council (2018), online: <<https://policybase.cma.ca/documents/Briefpdf/BR2019-02.pdf>>.

¹⁰⁶⁹ Health Canada. *A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare*. (2019).

Act (and its hospital-related restrictions) – and instead explicitly emphasizing the term Essential Medicines.¹⁰⁷⁰

The Hoskins Report also takes the very noteworthy step of expressly proposing a Canadian Essential Medicines List as an interim step towards pharmacare.¹⁰⁷¹ Before developing a full national formulary that would be covered by the pharmacare program, the Hoskins Report recommends creating a Canadian EML, part of a plan that would, at its completion, result in two lists to fill two longstanding gaps in Canadian pharmaceutical policy:

Given the transformation necessary for national pharmacare, and the time required to build a national formulary, it is practical to consider a phased approach to implementing pharmacare. This phased approach could take different paths, however the council recommends beginning with a carefully chosen list of essential medicines, available to all Canadians, as the first step towards a fully comprehensive list of drugs. This will enable a meaningful and early start to national pharmacare, since evaluating and negotiating prices for the complete formulary will take some time. The list of essential medicines—the most commonly prescribed clinically important drugs—would likely account for about half of all prescriptions dispensed in Canada.¹⁰⁷²

A number of observations can be drawn from this. First, this is a clear illustration of how different drug lists can not only do different things, but can be used in tandem. Furthermore, as noted early in this thesis, the Hoskins Report’s clear distinction between a formulary and an EML in the Canadian context is a valuable one. The Report clearly positions Essential Medicines as being more important than some other medicines that would nevertheless still deserve a spot on the national

¹⁰⁷⁰ Indeed, although the *Canada Health Act* is mentioned frequently in the Hoskins Report, “medically necessary” is mentioned only within a verbatim quote from the National Forum.

¹⁰⁷¹ This is not in fact a totally novel idea; for instance, a similar idea was floated by the Citizens’ Reference Panel on Pharmacare in Canada, noted above.

¹⁰⁷² Health Canada. *A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare*. (2019) p.76.

formulary, which in turn would exclude yet further medicines that would nonetheless be available on the Canadian market (and perhaps covered via additional insurance coverage). In doing so, it essentially adopts the proposed Canadian EML as a baseline or floor, with the national formulary as the ceiling for pharmacare coverage. This is a helpful conception of the difference between the two lists; it also illustrates why having both lists – having both a floor and a ceiling – is valuable for building pharmacare.¹⁰⁷³

Also important, of course, is the Hoskins Report’s definition of Essential Medicines in the context of a Canadian EML as “the most commonly prescribed clinically important drugs”. This definition deviates somewhat from the WHO definition of Essential Medicines as “those that meet the priority health care needs of the population and should be available within the context of functioning health systems at all times in adequate amounts and at a price the individual and the community can afford” cited by the Hoskins Report, but not by so much that the resemblance isn’t discernible. It also hybridizes the different approaches raised in the Advisory Council’s discussion paper.¹⁰⁷⁴ The sources that the Hoskins Report suggests using as a foundation for this Canadian EML offer some idea of how these different approaches might be applied, while also raising further questions:

There are two lists we think the Canadian drug agency should use as a starting point for creating the initial essential medicines list: the World Health Organization’s Model List of Essential Medicines (which has approximately 450 drugs) and the CLEAN Meds list (with 136 drugs) developed by clinicians and researchers at St. Michael’s Hospital in

¹⁰⁷³ Distressingly, it’s not at all clear that this differentiation between two kinds of drug list has penetrated the views of other parties pontificating on pharmacare. For instance, a 2020 report on the issue written by KPMG explicitly in response to the Hoskins Report bizarrely begins by noting that it will cover “implementation of an essential medicines list (‘EML’), or national formulary (both terms will be used interchangeably throughout the article),” an interpretation quite at odds with what the Hoskins Report actually says. KPMG, *Getting the list right: Development of an essential medicines list for Canada* (KPMG in Canada, 2020), online:

<<https://assets.kpmg/content/dam/kpmg/ca/pdf/2020/03/getting-the-list-right-en.pdf>>.

¹⁰⁷⁴ Advisory Council on the Implementation of National Pharmacare, *Towards Implementation of National Pharmacare Discussion Paper*, Discussion Paper, by Advisory Council on the Implementation of National Pharmacare, Discussion Paper (2018) at p.12.

Toronto. The drugs selected for the initial formulary should also be aligned with the national formulary's guiding principles.¹⁰⁷⁵

This is an intriguing juxtaposition, as these two suggested lists themselves do different things; rather than having complementary roles, as with the Canadian EML and national formulary, this approach melds them together. The WHO MEML lists the most important drugs at the global level. The CLEAN Meds list is very focused on the most widely used drugs in a Canadian primary care setting. Juxtaposing the two, one can see the intent to identify “the most commonly prescribed clinically important drugs”.¹⁰⁷⁶ However, a list focused upon the most widely used drugs in a Canadian primary care setting will by definition de-emphasize drugs serving smaller populations; this of course implicates drugs for Neglected Diseases.

In bringing these two lists together, the Hoskins Report offers its own evaluative framework. As it notes, the suggested principles are “based on those considered by formulary review committees across Canada, including those at CADTH and INESSS”.¹⁰⁷⁷ These four principles are:

- the clinical benefit it offers patients;
- its value for money;
- its alignment with patient and societal values, including diversity and equity considerations; and
- its broader impact on health care and health outcomes.¹⁰⁷⁸

¹⁰⁷⁵ Health Canada. *A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare* (2019) p.77.

¹⁰⁷⁶ Health Canada. *A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare* (2019) p.76.

¹⁰⁷⁷ The Canadian Agency for Drugs and Technologies in Health and Québec's Institut national d'excellence en santé et services sociaux, respectively. Canada & Health Canada. *A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare*. (2019) p.79.

¹⁰⁷⁸ Health Canada. *A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare* (2019) p.79.

These principles offer the opportunity to highlight not merely the differences between the two lists proposed as the basis of a Canadian EML, but the necessity of recognizing that some drugs found on the WHO MEML are not found in Canada in the first place. By the first of these standards, clinical benefit, Essential Medicines for Neglected Diseases like albendazole and artesunate would readily qualify; others might offer less benefit in absolute terms but remain the gold standard for treatment in the absence of superior alternatives. By the second, value for money, the cost might vary depending on source – highlighting the need for options other than Rodelis and Turing – but, particularly at global prices, value for money is likely to be notably higher than for a considerable number of other non-Essential Medicines used in Canada. By the third criterion of patient and societal values, including diversity and equity considerations, drugs used to treat conditions that disproportionately affect marginalized and minority communities would also be a good fit. Indeed, the diversity and equity provisions in particular underscore important considerations that should be at play when drugs of proven utility are already available internationally, and are in some cases funded by Canada elsewhere but are not formally available in this country. It is primarily on the fourth criterion that currently unmarketed Essential Medicines for Neglected Diseases might stumble, serving, as they often do, small populations. In some instances, such as staving off the spread of DR-TB, addressing a small number of cases may have a wider impact on health. In others, however, the impact on healthcare and health outcomes might be considerable for a particular community, but small within the grand scheme of things in Canada. This is of course already a factor that influences availability of medicines in the first place. However, this last point also underscores the gulf between a WHO-listed Essential Medicine not making the cut for a Canadian EML, which may be reasonable, and that drug not being formally available in Canada at all, which is not. This piece of the puzzle must not be overlooked; different lists of medicines play different roles, and examining the relationship of the WHO MEML to Canadian lists requires actually examining each of these standard of care Essential Medicines and the populations they serve in Canada.

So where does the Hoskins Report approach, balancing these four principles against “the most commonly prescribed clinically important drugs,” leave Essential Medicines for serious but less common Neglected Diseases, even those that are marketed in Canada? Additional considerations are raised via another major recommendation of the Hoskins Report that will be revisited: that Canada adopt a national strategy for expensive drugs for Rare Diseases. This is identified as a distinct priority, parallel to the Canadian EML itself, with the report proposing “that national pharmacare begin [...] with a formulary initially covering a list of essential medicines (together with a distinct process and dedicated funding for expensive drugs for rare diseases)”.¹⁰⁷⁹ Indeed, drugs for Rare Diseases are deemed sufficiently worthwhile that this “critically important initiative” came backed with \$500 million per year in the federal budget.¹⁰⁸⁰ As the explicit reference to “expensive drugs” suggests, the focus of the Rare Diseases component is on cost as a barrier to access, not market presence; this is despite the fact that market presence is an issue for Rare Disease drugs as well. However, taking a step back, the underlying purpose of this Rare Disease strategy is to ensure that, within the broader implementation of pharmacare, small groups of patients are also able to get access to the drugs they need. This goal could, and should, be extended to Neglected Diseases. After all, if Canada can devote hundreds of millions of dollars per year to ensuring access to expensive medicines for one set of small populations, as a key measure to be implemented in tandem with a Canadian EML (and before the implementation of a national formulary) as part of a healthcare expansion building towards pharmacare, this is a clear sign that Canada could also devote resources to ensuring proven Essential Medicines are available to other small populations.

It must of course be noted that the timeline proposed in the Hoskins Report for the creation of a Canadian EML has not been met, even with caveats built in: “Given that we have waited for national pharmacare for over 50 years, it makes

¹⁰⁷⁹ Health Canada. *A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare* (2019) p.88.

¹⁰⁸⁰ Health Canada. *A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare* (2019) p.11.

sense to take a little longer to get it right. We believe the essential medicines list can be ready for January 1, 2022, and a comprehensive national formulary should be in place no later than January 1, 2027.”¹⁰⁸¹ This timeline was echoed favourably by the Standing Committee on Finance in its February 2021 report.¹⁰⁸² However, the pharmacare initiative has since stumbled, with pharmacare largely absent from the 2021 budget.¹⁰⁸³ The exception to this shift, however, was the retention of \$500 million in funding for expensive rare diseases.¹⁰⁸⁴ After being largely absent from the governing Liberals’ election campaign in 2021, however, it resurfaced as part of an agreement between the NDP and the Liberals in 2022. Under this arrangement, the parties agree to pass a Canada Pharmacare Act by the end of 2023, *after* which the National Drug Agency will be tasked with developing “a national formulary of essential medicines”, a description rather ambiguous in its outcome.¹⁰⁸⁵ All of this demonstrates a few things: For one, experts believe a tailored Canadian EML *could* be developed in a relatively short period of time, though it requires political will. For another, Canada is fully capable of prioritizing, and funding, efforts get important drugs to small numbers of people who need them, whether or not this priority is included within or separate from pharmacare. And finally, that Essential Medicines look to remain part of the evolving pharmacare conversation.

¹⁰⁸¹ Health Canada. *A prescription for Canada: achieving pharmacare for all: final report of the Advisory Council on the Implementation of National Pharmacare* (2019) p.78.

¹⁰⁸² Standing Committee on Finance, “Investing in Tomorrow: Canadian Priorities for Economic Growth and Recovery: Report of the Standing Committee on Finance” (February 2021) 43rd Parliament, 2nd Session, online: <<https://www.ourcommons.ca/Content/Committee/432/FINA/Reports/RP11058298/finarp01/finarp01-e.pdf>>.

¹⁰⁸³ Government of Canada, “Budget 2021 A Recovery Plan for Jobs, Growth, and Resilience”, Online: <<https://www.budget.gc.ca/2021/home-accueil-en.html>>.

¹⁰⁸⁴ Indeed, the only actual number tied to pharmacare initiatives in the 2021 budget is that “the government will proceed with its announced plan to provide ongoing funding of \$500 million for the program for high-cost drugs for rare diseases” (p.238). Government of Canada, “Budget 2021 A Recovery Plan for Jobs, Growth, and Resilience”, Online: <<https://www.budget.gc.ca/2021/home-accueil-en.html>>.

¹⁰⁸⁵ Government of Canada (Prime Minister’s Office), “Delivering for Canadians Now”, (22 March 2022), *PMO News Releases* online: <<https://pm.gc.ca/en/news/news-releases/2022/03/22/delivering-canadians-now>>.

An Essential Medicines List for Canada

While there have long been proponents of an EML in Canada, the Hoskins Report is the closest it has come to direct integration into Canadian domestic policy.

Engaging with the WHO MEML and adopting a Canadian EML could play a valuable role in achieving Canadian pharmaceutical policy goals well beyond those relating to access to off-patent Essential Medicines for Neglected Diseases. Potential applications, with varying degrees of adaptation, range from laying a floor for pharmacare, to tackling drug shortages, to establishing a benchmark for meeting Canada's international commitments around the SDGs. So how might a Canadian EML be constructed? And how might this be done to ensure that Neglected Diseases are not neglected in the process?

That the WHO MEML was intended to be a tool of universal applicability has been discussed already. Nonetheless, concerns have been raised about Canadian perceptions of the WHO MEML, for instance by Eom and colleagues, who wrote in favour of establishing a Canadian EML but acknowledged that "many might argue" that a wealthy country like Canada has no need of one, and that an EML is a tool only for countries with less-developed health systems.¹⁰⁸⁶ The MEML's inclusion of numerous drugs for tropical diseases and other Neglected Diseases not normally associated with the priority health needs of Canadians may even fuel this perception, adding a layer of irony to lack of access to those very drugs. A 2019 study by Jarvis and colleagues on perceptions of a Canadian EML elaborates upon some potential reasons why the concept has historically generated little forward momentum. Interviews with cross-sectoral subjects revealed the following:

Some did not view an essential medicines list as applicable in the Canadian context, owing to a perceived difficulty in agreeing on a set of medicines that would sufficiently cover the needs of all Canadians or owing to an association of the concept with WHO and lower-income

¹⁰⁸⁶ Eom, Gina, Paul Grootendorst & Jacalyn Duffin. "The case for an essential medicines list for Canada" (2016) 188:17–18 CMAJ E499–E503, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.160134>>.

countries. Those who voiced a more global view of essential medicines voiced less opposition to an essential medicines list and saw this idea as synonymous with a formulary or as a “specific kind of formulary”.¹⁰⁸⁷

Indeed, even use of the term Essential Medicines List was identified in this study as a potential barrier to its acceptance, given the existing associations of the term with low-income countries.¹⁰⁸⁸ Other interviewees thought an EML might result in some Canadians receiving less coverage than under their current insurance plans, or that people would object to their choice being restricted.¹⁰⁸⁹ Such unfounded fears are a problem that has afflicted the WHO MEML for decades.¹⁰⁹⁰ As noted earlier, this attitude is reflected in Canadian legal scholarship operating from a similar presumption that Canada already has access to the WHO-listed Essential Medicines it requires, thus making the WHO MEML insufficient for the needs of the Canadian healthcare system.¹⁰⁹¹ Similar arguments about the MEML as a tool for LMICs have continued to impact its use in other high-income countries as well.¹⁰⁹² Once again, such views conflate the concepts of an EML (a floor) with other lists like a formulary (a potential ceiling); as such, it is a further demonstration of the value of clarifications like that provided in the Hoskins Report regarding the differences between different lists in a Canadian context.

Ultimately, Jarvis and colleagues don’t raise the issue of access to drugs for Neglected Diseases in Canada, once again demonstrating how thoroughly this issue

¹⁰⁸⁷ Jarvis, Jordan D et al. “Acceptability and feasibility of a national essential medicines list in Canada: a qualitative study of perceptions of decision-makers and policy stakeholders” (2019) 191:40 CMAJ E1093–E1099, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.190567>>.

¹⁰⁸⁸ Jarvis, Jordan D et al. “Acceptability and feasibility of a national essential medicines list in Canada: a qualitative study of perceptions of decision-makers and policy stakeholders” (2019) 191:40 CMAJ E1093–E1099, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.190567>>.

¹⁰⁸⁹ Jarvis, Jordan D et al. “Acceptability and feasibility of a national essential medicines list in Canada: a qualitative study of perceptions of decision-makers and policy stakeholders” (2019) 191:40 CMAJ E1093–E1099, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.190567>>.

¹⁰⁹⁰ For a prominent early example in the American context, see Lasagna, Louis. “The World Health Organization List of ‘Essential Drugs’” (1980) 93:2 Ann Intern Med 368, online: <<http://annals.org/article.aspx?doi=10.7326/0003-4819-93-2-368>>.

¹⁰⁹¹ Da Silva, Michael, “A Goal-Oriented Understanding of the Right to Health Care and its Implications for Future Health Rights Litigation” (2016) 39:2 Dal LJ 377.

¹⁰⁹² For instance, Australia. See Duong, Mai et al., “Essential Medicines in a High Income Country: Essential to Whom?” (2015) 10:12 PLoS One e0143654. <<http://annals.org/article.aspx?doi=10.7326/0003-4819-93-2-368>>.

is overlooked. Perhaps providing this information would have impacted the views of the interview subjects. At the same time, many interviewees remarked that an EML would become more acceptable to key parties by clearly emphasizing it as a means to improve equitable access to evidence-based, high-quality and affordable medicines.¹⁰⁹³ All of this suggests that some of the barriers to acceptance of a Canadian EML have been more about inaccurate perceptions of the WHO MEML than the real-world utility of an EML itself.

Under such circumstances, a practical demonstration of an EML in the Canadian context may be more helpful than abstract discussion. Unfortunately, despite the timelines of the Hoskins Report, no such list materialized in January 2022. This means that at the moment, the CLEAN Meds List highlighted alongside the WHO MEML in the Hoskins Report provides the most tangible example of such a list. Furthermore, it has already proven influential, being referenced not only by the Hoskins Report but also governmental bodies like the PMPRB. At the same time, the CLEAN Meds List has its own limitations making it unsuitable to assume the mantle of a Canadian EML, particularly when it comes to the problem of standard of care Essential Medicines vital for the treatment of small populations not being formally available in Canada. While its positive aspects should be acknowledged, Canadian integration of the Essential Medicines concept must go beyond the CLEAN Meds List.

CLEAN Meds List

The CLEAN Meds List is a Canadian academic project producing very similar but not quite identical lists of overlapping authorship, and in turn exploring their practical utility.¹⁰⁹⁴ For instance, the initial list, developed by Taglione and

¹⁰⁹³ Jarvis, Jordan D et al. "Acceptability and feasibility of a national essential medicines list in Canada: a qualitative study of perceptions of decision-makers and policy stakeholders" (2019) 191:40 CMAJ E1093–E1099, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.190567>>.

¹⁰⁹⁴ For instance, these three lists, with overlapping authorship, yield final lists of 117, 128, and 125 drugs, respectively: Morgan, Steven G et al., "Estimated effects of adding universal public coverage of an essential medicines list to existing public drug plans in Canada" (2017) 189:8 CMAJ E295–E302, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.161082>>; Persaud, Navindra et al., "Effect on Treatment Adherence of Distributing Essential Medicines at No Charge: The CLEAN Meds Randomized Clinical Trial" (2020) 180:1 JAMA Intern Med 27, online: <<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2752366>>; Taglione,

colleagues in 2017, offers 125 drugs.¹⁰⁹⁵ Another paper draws upon this list to estimate costs for 117 drugs, and compare them to costs in other countries; it finds the resulting list “accounted for 44% of all prescriptions and 30% of the total cost” in Canada in 2015.¹⁰⁹⁶ A further study found that supplying the 128 medicines on its own iteration of the CLEAN Meds List free of charge to Canadian patients was shown to improve adherence.¹⁰⁹⁷ Thus, the CLEAN Meds List idea has been used both to project costs of implementing drug coverage, and to empirically demonstrate links to better patient outcomes via that coverage.¹⁰⁹⁸ Importantly, it has also been recognized by part of Canada’s pharmaceutical regulatory apparatus. As noted earlier, in 2017 the PMPRB conducted a survey of the alignment between provincial formularies. When the PMPRB narrowed their analysis to drugs found on the CLEAN Meds List, pan-provincial coherence was far higher, with over 90% of the CLEAN Meds List drugs covered on average.¹⁰⁹⁹ This illustrates that the CLEAN Meds List does effectively capture what drugs are already being widely used across the country; it also shows that federal government bodies are open to using it as a point of reference. At the same time, the CLEAN Meds List is a very limited list. This is not necessarily a negative in and of itself; as noted elsewhere in this thesis, the WHO MEML has been adapted not merely for different countries but for different circumstances, with the 14 drugs of the basic version of the Interagency Emergency Health Kit as an extreme example. As a Canadian EML, however, it would be strikingly and indeed inappropriately brief.

Michael S et al., “Development of a preliminary essential medicines list for Canada” (2017) 5:1 CMAJ Open E137–E143, online: <<http://cmajopen.ca/lookup/doi/10.9778/cmajo.20160122>>.

¹⁰⁹⁵ Taglione, Michael S et al., “Development of a preliminary essential medicines list for Canada” (2017) 5:1 CMAJ Open E137–E143, online: <<http://cmajopen.ca/lookup/doi/10.9778/cmajo.20160122>>.

¹⁰⁹⁶ Morgan, Steven G et al. “Estimated effects of adding universal public coverage of an essential medicines list to existing public drug plans in Canada” (2017) 189:8 CMAJ E295–E302, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.161082>>.

¹⁰⁹⁷ Persaud, Navindra et al., “Effect on Treatment Adherence of Distributing Essential Medicines at No Charge: The CLEAN Meds Randomized Clinical Trial” (2020) 180:1 JAMA Intern Med 27, online: <<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2752366>>.

¹⁰⁹⁸ For the purposes of this thesis, further discussion will treat all of these lists in the aggregate as the CLEAN Meds List.

¹⁰⁹⁹ Patented Medicine Prices Review Board, *Alignment among public formularies in Canada, part 1*. (2017).

It immediately seems unintuitive that a list only slightly more than a quarter of the length of the 479 drugs found on the current WHO MEML should establish the floor for access by all the denizens of an upper-income country. After all, the perceived paucity of drugs on the WHO MEML is already viewed by some as a disincentive to adopting an EML in Canada; cutting it down by over two thirds is unlikely to assuage such fears. Comparing the two lists directly is slightly misleading, of course. The brevity of the CLEAN Meds List is explained in part by the fact that the gap it is trying to fill is one that exists within Canada's pre-existing artificial hospital/non-hospital divide. As such, a nebulous number of "medically necessary" drugs covered by the *CHA* may be absent from the list, provided they are medically necessary in a hospital setting and not widely used outside of hospitals. The perpetuation of this artificial divide means those medically necessary drugs do not receive the other benefits of listing on an EML, starting, rather basically, with their explicit identification, the starting point for a wide range of possible legal and policy interventions. This must be kept in mind when examining the development of the CLEAN Meds List.

There are other shortcomings to the CLEAN Meds List as a proxy for an EML. Consider the initial (125 drugs) iteration of the CLEAN Meds List, which includes the most detailed explanation of how the list was developed.¹¹⁰⁰ The foundation of that list is the 2013 WHO MEML; thus, there is an explicit link between the concepts, a positive starting point. From this starting point, the CLEAN Meds List adds medicines not found on the WHO MEML, but drawn from Canadian clinical practice guidelines, health technology assessment reports and similar international resources.¹¹⁰¹ This too is an appropriate method of adaptation. The creators of the list also sought to "identify the medicines on the WHO list that are applicable to

¹¹⁰⁰ Taglione, Michael S et al., "Development of a preliminary essential medicines list for Canada" (2017) 5:1 CMAJ Open E137–E143, online: <<http://cmajopen.ca/lookup/doi/10.9778/cmajo.20160122>>.

¹¹⁰¹ Taglione, Michael S et al. "Development of a preliminary essential medicines list for Canada" (2017) 5:1 CMAJ Open E137–E143, online: <<http://cmajopen.ca/lookup/doi/10.9778/cmajo.20160122>>.

Canada”.¹¹⁰² This too is in keeping with the MEML, which after all is intended as a Model for countries to adapt. Accordingly:

Removals from the WHO list were made for 1 of 5 reasons: items were not medications [e.g., condoms], other medications on the list had better tolerated routes of administration (e.g., oral medication available instead of intravenous), the medications had the same indication as other listed medications, the medications were used for conditions that are uncommon in Canada or the medications were not medications prescribed by primary care providers.¹¹⁰³

These justifications all have their merits, depending on the circumstances. The first three in particular seem entirely reasonable. However, the last two, focusing on uncommon conditions and medicines not prescribed by primary care providers, also raise questions. To begin with the final consideration, a shorter list makes sense if the intent is a list solely for primary care; after all, Halfdan Mahler, the WHO Director-General who shepherded the formalization of the Essential Medicines concept, had himself suggested a basic list of 30 drugs would suffice for primary healthcare.¹¹⁰⁴ However, it was also clear Mahler’s primary care list would only be a subset of the WHO MEML; indeed, the idea of explicitly compiling such a sublist for primary care was actually rejected by the WHO Expert Committee during the development of the inaugural WHO MEML in 1977.¹¹⁰⁵ As a primary care

¹¹⁰² Taglione, Michael S et al. “Development of a preliminary essential medicines list for Canada” (2017) 5:1 CMAJ Open E137–E143, online: <<http://cmajopen.ca/lookup/doi/10.9778/cmajo.20160122>>.

¹¹⁰³ Taglione, Michael S et al. “Development of a preliminary essential medicines list for Canada” (2017) 5:1 CMAJ Open E137–E143, online: <<http://cmajopen.ca/lookup/doi/10.9778/cmajo.20160122>>.

¹¹⁰⁴ Mahler, Halfdan. “The Meaning of ‘Health for All by the Year 2000’” (2016) 106:1 American Journal of Public Health 36–38.

¹¹⁰⁵ WHO Expert Committee. *The selection of essential drugs*, Technical report series / World Health Organization 615 (World Health Organization, 1977) p. 13. That said, the concept has been raised since that time. For instance, a model primary care list, consisting of 22 drugs that could be administered by health workers with little training, was included alongside the MEML in 1983. However, it remained distinct from the WHO MEML itself. WHO Expert Committee on the Selection

subset of Essential Medicines in Canada, 125 medicines may well be appropriate; this would be more than four times longer than some of the earlier primary care sub-lists that have been proposed for low-resource environments, and thus *prima facie* suggestive of the greater level of access that would be expected in the Canadian health system well into the 21st Century. As a complete Canadian EML, however, even one restricted to use outside the hospital setting, it would be remarkably and indeed inappropriately brief.

Other commentators have remarked on the absence of important drugs for more specialized conditions. For instance, while identifying the CLEAN Meds List as a useful prompt in the discussion around a national list of Essential Medicines in Canada, Barr suggests “their contributions are limited by the self-imposed restrictions to the prescribing practices of family physicians”.¹¹⁰⁶ Barr then goes on to provide examples, including how only one of nine drugs added to the WHO MEML for Children for the treatment of cancer is included in the proposed Canadian list.¹¹⁰⁷ The dearth of even formally marketed drugs for conditions like TB – not merely the world’s most prolific infectious killer prior to COVID-19, but as already highlighted a particular menace to marginalized communities within Canada – points to ways this rather barebones list could draw more fully on the WHO MEML to provide an EML going beyond the most commonly used drugs to offer important drugs better meeting the specific needs of a wider range of populations, particularly vulnerable populations, outside a hospital setting.¹¹⁰⁸

This ties into the other concerning criterion for removal from the Clean Meds List: that it is a drug for an uncommon condition. It is striking that in the development of the CLEAN Meds List, the only example mentioned by name amongst the 52 drugs found on the WHO MEML that were removed from the initial

and Use of Essential Medicines, *The use of essential drugs*, Technical report series / World Health Organization 685 (1983).

¹¹⁰⁶ Barr, Ronald D. “List of essential medicines for Canada” (2017) 189:19 CMAJ E703–E703, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.732971>>.

¹¹⁰⁷ Barr, Ronald D. “List of essential medicines for Canada” (2017) 189:19 CMAJ E703–E703, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.732971>>.

¹¹⁰⁸ It does include the 2nd line drug levofloxacin, which is on the WHO MEML for drug-resistant TB, but that is not its usual indication. Indeed, it is not formally indicated for TB in Canada; however, it is included within the Canadian Tuberculosis Standards.

CLEAN Meds List for being for “uncommon indications in Canadian primary care” is ivermectin.¹¹⁰⁹ Even more striking is the lack of acknowledgment that at the time the CLEAN Meds List was being compiled, this Essential Medicine found in Canadian treatment guidelines was not formally available in Canada at all. This underscores yet again how treatments for Neglected Diseases are neglected even by those actively developing a medicines list to help enable access to medicines in Canada. There is a massive gulf between “most commonly used in primary care” and “standard of care drug that is not formally available”. This points to an important complementary role that the WHO MEML should play.

Developing a Canadian EML

A portion of the value of developing a Canadian EML, if done properly, would thus extend beyond the Canadian EML itself. This further value would arise via the explicitly assessment of the WHO MEML alongside treatment guidelines within the Canadian context. As this suggests, the underlying *process* of developing a Canadian EML is a crucial element. Rather than focusing solely on the endpoint of a Canadian EML, this would involve cataloguing the Canadian market status of drugs deemed Essential Medicines at the international level. This assessment of the WHO MEML within the Canadian context would go both ways. If there are gaps on the WHO MEML that are particularly salient for the Canadian context, they should be filled with additional medicines (as they are on the CLEAN Meds List); this is particularly appropriate given Canada’s ample resources. At the same time, having to explicitly address each drug already on the WHO MEML will require engagement with drugs that are currently overlooked, exemplified by those for Neglected Diseases. The process should be thorough and transparent. It should raise important questions, and seek an evidentiary base in answering them. Is a drug medically useful to Canadian patients? If so, is it formally available to them?¹¹¹⁰ The end result should

¹¹⁰⁹ Taglione, Michael S et al. “Development of a preliminary essential medicines list for Canada” (2017) 5:1 CMAJ Open E137–E143, online: <<http://cmajopen.ca/lookup/doi/10.9778/cmajo.20160122>>.

¹¹¹⁰ Without going overboard in suggesting avenues of exploration, a wide range of considerations might be pertinent. Is this drug featured in Canadian or international guidelines? Does it currently form the standard of care at home or abroad? Are there equally effective (or superior) alternatives

be that every drug on the WHO MEML is explicitly accounted for. To be clear, a drug's appearance on the WHO MEML does not mean it should automatically appear on the Canadian EML. It also does not mean it should appear on the national formulary. In fact, it may not even mean it needs to be formally marketed in Canada at all. However, as a first step preceding further interventions, its formal availability should be clarified and justified.

This process should also not be a one-time thing. For instance, a logical timeline for renewing the Canadian EML would be to do so in connection with the WHO MEML, which is updated roughly every two years; evidence assembled for the MEML could also inform Canadian decisions. This parallel review should apply at the very least to new additions to the MEML, as well as novel indications. At the same time, deletions of medicines (and indications) from the MEML should serve as a prompt to reflect on Canadian policy and practice. Lastly, directly adapting the WHO MEML in this fashion would serve another important purpose at the international level: sending a message of solidarity on Essential Medicines. It would show Canada believes not only in the Essential Medicines concept and the WHO MEML, but in operationalizing it. This would not only aid Canada in meeting its ICESCR obligations, but provide a reference point for evaluating its performance in areas like the SDGs. As discussed further later on, formalizing Canadian links to the WHO MEML could in turn be further connected to other initiatives, ranging from foreign aid projects to international cooperation on regulatory standards for drugs useful not only abroad but, quite explicitly, at home.

Developing and maintaining a Canadian EML tied to the WHO MEML (and to other reference points like treatment guidelines) would thus serve as a springboard for numerous useful initiatives, including: providing a floor for consistent pan-Canadian drug coverage; identifying drugs important for healthcare and thus requiring special attention to address any risk of shortages or attrition

available in its stead? Does Canada support access to this drug in its international programming? How many Canadian patients require this drug in an average year? Are any marginalized groups overrepresented among those patients? If a drug is not formally available in Canada, has there been any attempt by the company to bring it to market in the past? If there hasn't, what steps if any have been taken to address this state of affairs?

from the market; providing a metric for Canada to measure its progress in meeting international goals like the SDGs; and identifying and cataloguing drugs not formally available in Canada. However, for the purposes of this thesis, it is the identification and justification of the market status of Essential Medicines that is the most important. A clear demonstration that the recognized standard of care is not readily available for patients who need them should in turn require a response. The question remains whether improving access to such drugs will come via attempts to improve means of accessing unmarketed drugs, or by taking steps to bring them formally to market. The past few years have seen advances on both fronts, suggesting at the very least that change is possible. Before exploring these two broad alternatives, however, it is important to emphasize one further area of pharmaceutical policy highly relevant to Neglected Diseases.

Chapter 10: Reconciling Neglected and Rare Diseases

Unapproved drugs for small populations

In the past few years, Canada has in fact directed increased attention towards access to treatment for a group of diseases that affect small numbers of Canadians. Historically, pharmaceutical companies have devoted little attention to developing treatments for these diseases. In turn, where treatments do exist, those companies have declined to bring them to the Canadian market, citing unfavourable market conditions. As a result, access to treatment has often depended heavily on the Special Access Programme. The diseases in question are not Neglected Diseases, however, but another category of disease: Rare Diseases.

The measures focused on high-priced drugs for Rare Diseases included in parallel with the construction of a Canadian EML in the Hoskins Report are a prime example of the attention being directed towards access to medicines for these conditions. In taking steps to improve access to medicines for Rare Diseases, Canada also follows belatedly in the footsteps of other higher income jurisdictions, from the US to the EU, that have already enacted laws geared to similar ends. Despite some key differences between the two groups of diseases, such attention to Rare Diseases could, and should, have implications for Neglected Diseases in Canada. This can be accomplished in part by recognizing the access challenges shared by both Rare Diseases and Neglected Diseases, such as reliance on the SAP for unmarketed drugs, and addressing the underlying barriers. However, given the momentum for action on the former and the ongoing neglect of the latter, in practical terms it may ultimately become necessary to instead continue the historical trend of squeezing Neglected Diseases into whatever access tools are available by framing them as Rare Diseases. Either way, it is useful to set out parallels between the two categories of disease.

Much like Essential Medicine and Neglected Disease, Rare Disease is a term with an intuitive component. However, it also raises a fundamental question: How “rare” is a Rare Disease? While Rare Disease is legally defined in some countries, such is not formally the case in Canada. A 2021 Health Canada discussion paper

begins by stating “There is no common internationally or even nationally accepted definition of what a rare disease is”.¹¹¹¹ This is true; those countries that do have a legislated definition approach the issue in different ways. For instance, the American definition uses an absolute number (less than 200,000 patients in the USA), while the EU uses a relative measure (less than 5 cases per 10,000 inhabitants).¹¹¹² Even though Canada has no codified definition, however, Parliamentary testimony from Health Canada – while again acknowledging there is no standard international definition of Rare Disease – has indicated Health Canada uses a definition in line with the EU, defining a Rare Disease as one that affects fewer than 5 in 10,000 Canadians.¹¹¹³ This is echoed in other Health Canada documents, though the figure is sometimes framed differently (e.g., 1 in 2000).¹¹¹⁴

It remains to be seen whether Canada will formalize a legal definition of Rare Disease as part of its increased interest in the topic, and if so, what the definition will be. Regardless of whether the mathematical dimension of a Rare Disease is defined in relative or absolute terms, however, the related question arises: If rarity is a defining feature, can Neglected Diseases also qualify as Rare

¹¹¹¹ Health Canada, *Building a national strategy for high-cost drugs for rare diseases: a discussion paper for engaging Canadians* (2021) at p.4.

¹¹¹² *Orphan Drug Act* of 1983, Pub L. No. 97-414, 96 Stat. 2049 as amended by the Health Promotion and Disease Prevention Amendments of 1984, Pub. L. 98-551, 98 Stat 2815 (1984), § 4; Art. 3(1)(a), *Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products*. It is worth observing that the American definition was added by amendment the year after the *Orphan Drug Act* was passed, rather than included in the original version.

¹¹¹³ It's worth noting this definition uses the vaguer “affected” rather than prevalence or incidence. Standing Committee on Health, *Canadians affected by rare diseases and disorders: Improving access to treatment*, 42nd Parliament, 1st Session (2019), online: <<https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf>> at p.7. At the same time, while there's a conversation to be had about prevalence versus incidence when it comes to infectious Neglected Diseases, there are examples of relevant legal definitions using prevalence, e.g., US FDA, “Designating Additions to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act” 80 FR 50559 (20 August 2015), online: <<https://www.federalregister.gov/documents/2015/08/20/2015-20554/designating-additions-to-the-current-list-of-tropical-diseases-in-the-federal-food-drug-and-cosmetic>>. If anything, however, the comparison of annual incidence of an infectious Neglected Disease with population prevalence of a Rare Disease only serves to underscore the disproportionate attention granted to the latter.

¹¹¹⁴ Health Canada, *Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework*, (13 December 2012), online: <<http://www.orpha.net/national/data/CA-EN/www/uploads/Initial-Draft-Discussion-Document-for-A-Canadian-Orphan-Drug-Regulatory-Framework.docx>>.

Diseases? If the definition is purely a numerical one, they would in Canada. Take malaria, one of the more common Neglected Diseases in Canada, and the close to 500 cases per year seen for much of this century; that would still qualify as affecting less than 5 in 10,000 Canadians.¹¹¹⁵ A steady figure of 1500-1700 cases of active TB seen over the same period would similarly qualify.¹¹¹⁶

Blurring lines even further, some quintessential Neglected Diseases would qualify as numerically rare even in endemic regions. For instance, the total number of cases of sleeping sickness reported worldwide (both *Tb rhodesiense* and *Tb gambiense*) dropped below 1000 in 2019, and even lower in 2020.¹¹¹⁷ By this count, the number of cases of sleeping sickness would qualify as rare not only globally, but in every endemic country. This is all the more the case for *Tb rhodesiense*, which accounts for less than 5% of reported cases.¹¹¹⁸ A purely numerical comparison is not perfect; given sleeping sickness is a disease with a history of epidemics, alongside other complicating factors like animal reservoirs and the potential for underreporting among the most affected populations, raw case numbers do not fully convey its public health importance. Nonetheless, even dramatic undercounting would be unlikely to reverse this trend.¹¹¹⁹ The fact that

¹¹¹⁵ Retrieved from Public Health Agency of Canada, "Reported cases from 1924 to 2019 in Canada - Notifiable diseases on-line", online: <<https://diseases.canada.ca/notifiable/charts?c=pl>>. As of this writing, Canada's population was estimated to be slightly under 38 million people.

¹¹¹⁶ Retrieved from Public Health Agency of Canada, "Reported cases from 1924 to 2019 in Canada - Notifiable diseases on-line", online: <<https://diseases.canada.ca/notifiable/charts?c=pl>>.

Tuberculosis does raise the interesting issue of latent infection, with some authors citing figures as high as 1.5 million people in Canada. See e.g., Essue, Beverley M, Deborah Milinkovic & Stephen Birch, "Better data to drive more effective care for people with latent tuberculosis infection in Canada" (2018) 190:23 CMAJ E700-E701. However, one could also argue a condition affecting 1 in 25 Canadians would in any case be deserving of more attention than it currently receives.

¹¹¹⁷ World Health Organization, "Trypanosomiasis, human African (sleeping sickness)" (10 January 2022), online: <[https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-\(sleeping-sickness\)](https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness))>.

¹¹¹⁸ World Health Organization, "Trypanosomiasis, human African (sleeping sickness)" (10 January 2022), online: <[https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-\(sleeping-sickness\)](https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness))>.

¹¹¹⁹ An even more extreme example of a rare Neglected Disease would be Guinea Worm (*Dracunculus medinensis*), a parasitic disease that went from over 3 million cases a year in the 1980s to just 14 in 2020; however, its near-eradication has been accomplished not with Essential Medicines but through other public health means. Kreier, Freda, "Just 14 cases: Guinea worm disease nears eradication" (2022) Nature, online: <<https://www.nature.com/articles/d41586-022-00385-z>>. See also Molyneux, David H et al., "Certifying Guinea worm eradication: current

this archetypal Neglected Disease could qualify, at least numerically, as a Rare Disease even in endemic countries aptly illustrates the issue of access to drugs for small populations. Further underscoring the parallel, the addition of fexinidazole to the WHO MEML in 2019 shows how Neglected Diseases, even present only in small numbers, still necessitate the innovation of new Essential Medicines.¹¹²⁰

The math shows that the parallels between Rare Diseases and Neglected Diseases add up in this regard at least. Crunching numbers further, another obvious parallel is that the public health impact of both groups of diseases is often framed in the aggregate; some estimates suggest one in twelve Canadians may suffer from a Rare Disease, while as many as one in six people worldwide could be afflicted

challenges" (2020) 396:10265 The Lancet 1857–1860, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673620325538>>.

¹¹²⁰ The inverse question is that of whether Rare Disease drugs can also be Essential Medicines. This issue is beyond the scope of this thesis. However, controversy over this issue tends to overlook the fact the inclusion of Rare Disease drugs was contemplated from the very first WHO MEML, with "treatment in rare disorders" explicitly flagged as complementary drugs that "should be available as funds permit". WHO Expert Committee. *The selection of essential drugs*, Technical report series / World Health Organization 615 (World Health Organization, 1977) at p.20. In turn, the first WHO MEML included drugs like fludrocortisone, used for the Rare Disease Addison's disease. The second WHO MEML in 1979 made explicit that some drugs were listed for "use in rare disorders or in exceptional circumstances". World Health Organization, ed, *The selection of essential drugs: second report of the WHO Expert Committee [on the Selection of Essential Drugs ; Geneva, 2 - 6 July 1979]*, Technical report series / World Health Organization 641 (Geneva, 1979) at p.10. And by 1988, it was clarified that in "certain situations there is a need to make available additional drugs essential for rare diseases". WHO Expert Committee on the Use of Essential Drugs, ed, *The Use of essential drugs: third report of the WHO Expert Committee*, Technical report series / World Health Organization 770 (Geneva : Albany, NY: World Health Organization ; WHO Publication Center USA [distributor], 1988). In truth, most controversy at the WHO level stems from a brief period in the early 2000s where there were attempts to remove Rare Disease drugs in the context of developing the 13th MEML, only for some to be subsequently retained by the 14th MEML. World Health Organization, ed, *The selection and use of essential medicines: report of the WHO expert committee, 2003 ; (including the 13th model list of essential medicines)* WHO Technical Report Series 920 (Geneva: World Health Organization, 2004); World Health Organization, ed, *The selection and use of essential medicines: report of the WHO Expert Committee, 2005 ; (including the 14th model list of essential medicines)* WHO technical report series 933 (Geneva, 2006). By the 18th MEML, this issue was revisited, and a series of considerations were adopted to explicitly accommodate Rare Disease drugs. Most notably, this included evidence of the effectiveness of the drug, such that "if a medicine is highly effective in relation to relevant outcomes – in terms of magnitude of effects or capacity to cure or control – for a particular condition, it has been more likely to be accepted as essential even if the target disease is relatively uncommon". WHO Expert Committee on the Selection and Use of Essential Medicines & World Health Organization, eds, *The selection and use of essential medicines: report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children)*, WHO technical report series 985 (Geneva, Switzerland: World Health Organization, 2014). This clarification in turn lends force to the importance of treating Essential Medicines for Neglected Diseases as essential even in low-burden settings.

with an NTD.¹¹²¹ Aggregate problems can foster aggregate solutions; rather than focusing on a single drug, the necessity of improving access to multiple drugs for multiple conditions becomes more obvious. This in turn demonstrates the value of reforms that would tackle the underlying issues around access to treatment for diseases, Rare or Neglected, that individually affect small numbers of people in Canada.

At the same time, other elements of what constitutes a Rare Disease are not always so readily quantifiable. Genetic conditions are the quintessential Rare Diseases, including conditions like Gaucher's disease, Wilson's disease, or Fabry disease; cystic fibrosis is among the most familiar diseases widely classified as Rare. The edges of the concept are considerably fuzzier; while it may sometimes be assumed that the term is being used to refer only to genetic conditions, this is not necessarily the case. The ambiguity around the definitional boundaries of Rare Diseases can be seen in Canada's 2021 consultation document on high-cost drugs for Rare Diseases, which states that approximately "80 percent of rare diseases have a genetic basis".¹¹²² The origins of the remaining 20% are left unaddressed. Meanwhile, other sources drawn upon by Canada do explore this issue in more detail. Consider Orphanet, an international information portal on Rare Diseases involving a consortium of over 30 countries including Canada.¹¹²³ With clear implications for Neglected Diseases, Orphanet's resources state both that a disease can be rare in one region but common in another, and that there are very rare infectious diseases.¹¹²⁴

¹¹²¹ See e.g., Health Canada, *Building a National Strategy for High-Cost Drugs for Rare Diseases* (2021) at p.4; Mitra, Amal K & Anthony R Mawson, "Neglected Tropical Diseases: Epidemiology and Global Burden" (2017) 2:3 *Trop Med Infect Dis*.

¹¹²² Health Canada, *Building a National Strategy for High-Cost Drugs for Rare Diseases* (2021) at p.4.

¹¹²³ The precise extent of Canada's current involvement in Orphanet is hard to determine. Canada announced its participation in 2012; content specific to the Canadian portal itself does not seem to have been updated since 2017, even if the international resources remain active. However, as of 2020, Health Canada resources refer to Canada being an "active member". Health Canada, "Canada's regulatory approach to drugs for rare diseases: orphan drugs" (3 July 2020), online: <<https://www.canada.ca/en/health-canada/services/licences-authorizations-registrations-drug-health-products/regulatory-approach-drugs-rare-diseases.html>>.

¹¹²⁴ Orphanet (Canadian entry point), "About rare diseases", online: <<http://www.orpha.net/national/CA-EN/index/about-rare-diseases/>>.

Interventions to improve access to treatment for Rare Diseases often rub up against Neglected Diseases in practice. For instance, many of the Neglected Diseases discussed in this paper, including tuberculosis, malaria, Chagas disease and sleeping sickness, have all qualified as rare under the American pharmaceutical regulatory regime.¹¹²⁵ Scholars too have drawn these parallels, including within the context of off-patent trolling and measures to address it.¹¹²⁶ However, in Canada these parallels remain obvious but largely unspoken. For instance, in the spring of 2018, the House of Commons Standing Committee on Health (HESA) adopted a motion to “undertake a study on the barriers to access to treatment and drugs for Canadians affected by rare diseases and disorders, including the Special Access Program, in order to develop recommendations on actions that the federal government can take, in partnership with the provinces and territories, to remove these barriers”.¹¹²⁷ While the hearing and subsequent report never explicitly clarify the status of Neglected Diseases, the blurring of the lines is quite evident in testimony before HESA. For instance, a single back-and-forth exchange between an MP and a Health Canada witness manages to cover the SAP-distributed Rare Disease drug Cystagon (a version of cysteamine, discussed later), the treatment of the Neglected Disease cutaneous larva migrans (treated with ivermectin or albendazole, discussed earlier), and the inability of Health Canada to make a company enter the Canadian market.¹¹²⁸ In the resulting report, HESA discusses some potential regulatory tools for improving access to medicines for Rare Diseases:

¹¹²⁵ In this case, in the context of orphan drug legislation, discussed shortly. US Food & Drug Administration, “Search Orphan Drug Designations and Approvals”, online: <<https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>>.

¹¹²⁶ See e.g., Beall, Reed F et al., “Generic Competition for Drugs Treating Rare Diseases” (2020) 48:4 J Law Med Ethics 789–795. This paper leads with a discussion of pyrimethamine and trientine, describing both as being for Rare Diseases.

¹¹²⁷ House of Commons Standing Committee on Health (HESA), Minutes of Proceedings, 1st Session, 42nd Parliament, 18 April 2018.

¹¹²⁸ The exchange is between MP Marilyn Gladu and Dr. John Patrick Stewart on 27 September 2018. The full exchange can be found here between the markers 0920 and 0925: <https://www.ourcommons.ca/DocumentViewer/en/42-1/hesa/meeting-112/evidence>.

A specific regulatory framework for rare disease treatments could include incentives to develop and commercialize drugs for rare diseases in Canada, an orphan drug designation process, additional market exclusivity, research promotion funds, tax incentives and regulatory submission fee reductions.¹¹²⁹

Building upon these ideas, HESA's specific recommendations range from reducing regulatory fees as a means to encourage manufacturers to seek market authorization to reforming the Special Access Programme.¹¹³⁰ Such ideas are readily applicable to Neglected Diseases as well. Furthermore, many of them could be applied not only to the development of new treatments, but access to old, off-patent ones; as discussed further below, often underemphasized is the fact that access to old medicines is also a major issue faced by many Canadian Rare Disease patients and their caregivers, just as it is for Neglected Diseases.

Even in the absence of clarity on this matter at the policy level, let alone a codified Canadian legal definition of Rare Disease, it is clear that responses to Rare Diseases and Neglected Diseases should not be segregated from each other. Even if the political impetus for reform lies with Rare Diseases, it makes little sense to be actively pursuing a strategy to improve access to treatment for Canadians afflicted with one set of uncommon diseases without including the other, particularly when the solutions overlap considerably. At the same time, if new pathways for tailored to Rare Disease drugs emerge, Neglected Diseases may once again find themselves relying on tools designed for other diseases simply because no better options are available.

¹¹²⁹ Standing Committee on Health, Canadians affected by rare diseases and disorders: Improving access to treatment, 42nd Parliament, 1st Session (2019), online: <<https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf>> at p.12-13.

¹¹³⁰ Standing Committee on Health, Canadians affected by rare diseases and disorders: Improving access to treatment, 42nd Parliament, 1st Session (2019), online: <<https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf>>.

Why are Rare Diseases treated differently?

There are a range of possible reasons why Rare Diseases receive attention that Neglected Diseases do not. One difference is the financial element. While both kinds of disease have small markets in Canada (and other HICs) in terms of patient numbers, it is only the market for Rare Diseases that has been increasingly viewed as a potentially lucrative one by pharmaceutical companies. In drawing this general comparison, it should be recognized that some drugs for Neglected Diseases are new and expensive (like the DR-TB Essential Medicines bedaquiline and delamanid, neither of which are marketed in Canada), while many Rare Diseases are treated with old, off-patent drugs, some examples of which will be discussed in more detail.¹¹³¹ However, high-priced drugs for Rare Diseases are such a recognizable issue that the strategy found in the Hoskins Report is focused upon them specifically.¹¹³² Two years later, even as the 2021 Federal Budget backed away from the national formulary and pharmacare, it maintained the emphasis – and, more importantly, half a billion dollars in spending – on high-cost Rare Diseases.¹¹³³

While the issue of market entry has also been an important topic for Rare Diseases in Canada, it has manifested somewhat differently than with Neglected Diseases. Particularly where high prices for Rare Disease drugs are accepted in foreign markets, the threat (express or implied) of not entering the Canadian market can be evoked – both by companies wanting to profit from drug sales and by patients concerned about being denied access – to push back against government measures to lower drug prices, such as reforms to the PMPRB. Indeed,

¹¹³¹ As an illustration, Janssen initially introduced bedaquiline at a cost of \$30,000USD for a six-month course of treatment in high-income countries (or at least those where it was brought to market in the first place). MSF Access Campaign, *DR-TB Drugs Under the Microscope*, 4th ed. (Médecins Sans Frontières, 2016), online: <<https://msfaccess.org/dr-tb-drugs-under-microscope-4th-edition>>.

¹¹³² Note the proposed strategy does not refer simply to “Drugs for Rare Diseases”. Health Canada, *Building a National Strategy for High-Cost Drugs for Rare Diseases* (2021)

¹¹³³ Indeed, the only actual number tied to pharmacare initiatives in the 2021 budget is related to Rare Diseases: “the government will proceed with its announced plan to provide ongoing funding of \$500 million for the program for high-cost drugs for rare diseases” (p.238). Government of Canada, “Budget 2021 A Recovery Plan for Jobs, Growth, and Resilience”, Online: <<https://www.budget.gc.ca/2021/home-accueil-en.html>>.

this strategy has been employed extensively in Canada.¹¹³⁴ Using market entry as political leverage also highlights some interesting facts about the Canadian pharmaceutical market as a whole. Depending what point one wishes to make, one can emphasize that Canada only accounts for roughly 2% of the global pharmaceutical market and thus is no great loss for pharma companies, or underscore that this number still places Canada within the top ten pharmaceutical markets in the world.¹¹³⁵ If broken down further, Canada's global market share is likely to be even more favourable for the global Rare Disease market (certainly by revenue), whereas its lower than average burden of most Neglected Disease decreases its appeal further.

Even as high-priced new drugs for Rare Diseases have simultaneously both inspired and undermined government efforts to lower patented drug prices via measures like a reformed PMPRB, Rare Diseases have been used to make the argument that cost itself should not be a major consideration in government determinations around access to medicines in the first place, with some scholars going so far as to argue the price tag simply should not be allowed to be a barrier to patient access in Canada at all. Panju and Bell, for instance, "advocate for an economic measure rooted in the rule of rescue: the imperative that, in the absence of alternative treatment, patients with life-threatening diseases should receive

¹¹³⁴ A very high-profile example was the delay by the pharmaceutical company Vertex in applying to Health Canada to approve its cystic fibrosis drug Trikafta (elexacaftor/tezacaftor/ivacaftor). Despite repeated statements by Health Canada that it was waiting on Vertex to submit an application, patient groups and pharmaceutical companies alike tied the delay to proposed reforms to the PMPRB. In the interim, some patients were able to access Trikafta via the SAP. See e.g., Iveson, John, "Iverson: The math of saving lives — Canada's drug battle leaves patients caught in the middle", *The Ottawa Citizen* (31 October 2020), online: <<https://ottawacitizen.com/opinion/john-iverson-the-math-of-saving-lives-canadas-drug-battle-leaves-patients-caught-in-the-middle/>>; Vertex Pharmaceuticals, Letter from Vertex Pharmaceuticals (Canada) Incorporated to the Patented Medicine Prices Review Board, "Re: Guidelines to operationalized changes to the *Patented Medicines Regulations*" (13 Feb 2020), online: <https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/submission-received/2020_02_Guideline_Consultation_Submission_Vertex_Pharmaceuticals_Canada.pdf>.

¹¹³⁵ As of May 2021, Industry Canada's website states "Pharmaceutical sales in Canada have a 2.1% share of the global market, making Canada the 9th largest world market". Industry Canada, "Pharmaceutical industry profile", online: *Government of Canada* <https://www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/h_hn01703.html>.

therapy irrespective of cost”.¹¹³⁶ In practice, coverage for Rare Disease drugs is not irrespective of cost in Canada, particularly when it comes to differing coverage decisions between provinces. In some cases, provinces have come to different conclusions about coverage, leading to unequal access across the country.¹¹³⁷ In others, however, there has been widespread acceptance of high costs. Consider eculizumab (tradename Soliris), a Rare Disease treatment that at one time was labelled the world’s most expensive drug.¹¹³⁸ It has been marketed in Canada since 2009 by Alexion and is approved for multiple indications. As of 2015, every province covered it for paroxysmal nocturnal hemoglobinuria patients (around 90 patients across the country).¹¹³⁹ Its list price at the time for this condition was \$500,000 annually, although provinces collectively negotiated a lower (but secret) price.¹¹⁴⁰ For treatment of another Rare Disease, atypical hemolytic uremic syndrome, it cost even more; it was later submitted in court that the total cost was between \$520,000 and \$700,000, annually, per patient.¹¹⁴¹ These prices were so high that they led to a hearing at the PMPRB. In the hearing, the PMPRB found the price of Soliris excessive under sections 83 and 85 of the *Patent Act* and ordered

¹¹³⁶ Panju, A H & C M Bell. “Policy alternatives for treatments for rare diseases” (2010) 182:17 Canadian Medical Association Journal E787–E792, online:

<<http://www.cma.ca/cgi/doi/10.1503/cma.081429>>.

¹¹³⁷ To use the example of Trikafta once again, Ontario, Alberta and Saskatchewan agreed in September 2021 to cover the drug; other provinces had yet to do so. The list price of the drug at the time was approximately \$300,000 per patient per year. Brege, Adina, “Ontario, Alberta and Saskatchewan to cover ‘life-changing’ cystic fibrosis drug”, *CTV News* (24 September 2021), online: <<https://www.ctvnews.ca/health/ontario-alberta-and-saskatchewan-to-cover-life-changing-cystic-fibrosis-drug-1.5600064>>.

¹¹³⁸ Blackwell, Tom, “World’s most expensive drug — which costs up to \$700,000 per year — too expensive, Canada says”, *The National Post* (3 February 2015), online: <<https://nationalpost.com/health/worlds-most-expensive-drug-prescription-that-costs-up-to-700000-per-year-too-expensive-canada-says>>.

¹¹³⁹ Blackwell, Tom, “World’s most expensive drug — which costs up to \$700,000 per year — too expensive, Canada says”, *The National Post* (3 February 2015), online: <<https://nationalpost.com/health/worlds-most-expensive-drug-prescription-that-costs-up-to-700000-per-year-too-expensive-canada-says>>.

¹¹⁴⁰ Blackwell, Tom, “World’s most expensive drug — which costs up to \$700,000 per year — too expensive, Canada says”, *The National Post* (3 February 2015), online: <<https://nationalpost.com/health/worlds-most-expensive-drug-prescription-that-costs-up-to-700000-per-year-too-expensive-canada-says>>.

¹¹⁴¹ *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)*, 2019 FC 734 at para 19.

Alexion to forfeit excess revenues.¹¹⁴² On judicial review, the Federal Court upheld the PMPRB decision in 2019.¹¹⁴³ However, in the summer of 2021, the decision was overturned by the Federal Court of Appeal.¹¹⁴⁴ This latter ruling occurred in the wake of the Supreme Court of Canada's landmark decision in *Vavilov*.¹¹⁴⁵ That precedent had implications for the FCA's willingness to defer to the PMPRB.¹¹⁴⁶ The FCA raised concerns that the PMPRB had gone beyond its statutory mandate, including by regulating the reasonableness of pricing rather than preventing excessive pricing.¹¹⁴⁷ In doing so, the FCA adopts a narrow interpretation of the Supreme Court's decision in *Celgene* (2011), discussed elsewhere in this thesis, in which, as it describes, "the Supreme Court loosely and occasionally speaks of these provisions having a consumer protection purpose and cites some politicians' speeches to that effect".¹¹⁴⁸ Ultimately, the FCA quashed the decision, and sent it back to the PMPRB.

Putting aside the legal merits of the case itself, however, one key takeaway from the Soliris saga is that Canada's apparatus for tackling high drug prices is not ideally suited to the task in its current form. As of this writing, there has been no closure to the question of whether a drug that was literally the most expensive in the world was excessively priced. Whatever the final outcome, it has been a slow and laborious trudge through an already infrequently used process. If the price of the most expensive drug in the world is the subject of lengthy examination, it is a sign that high drug prices for Rare Diseases are already normalized. In turn, a

¹¹⁴² *Patented Medicine Prices Review Board in the matter of the Patent Act*, R.S.C. 1985, c. P-4, as amended and in the matter of Alexion Pharmaceuticals Inc. and the medicine "Soliris" (2017), online: <http://www.pmprb-cepmc.gc.ca/CMFiles/Hearings%20and%20Decisions/Decisions%20and%20Orders/soliris_decision_public_version.pdf>.

¹¹⁴³ *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)*, 2019 FC 734.

¹¹⁴⁴ *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)*, 2021 FCA 157.

¹¹⁴⁵ *Canada (Minister of Citizenship and Immigration) v. Vavilov*, 2019 SCC 65.

¹¹⁴⁶ As the FCA says: "Had we considered this appeal before *Vavilov*, we would have had to consider whether we should Cooper up the Board's decision. But no longer. *Vavilov* recognizes the shortcomings in the former law and fixes them. It now requires us to ask if there is a sufficient reasoned explanation in support of the Board's decision. If there is not, the decision is unreasonable and must be quashed. Here, the Board's decision falls significantly short of the mark". *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)*, 2021 FCA 157 at para.10.

¹¹⁴⁷ *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)*, 2021 FCA 157 at para.11.

¹¹⁴⁸ *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)*, 2021 FCA 157 discussing *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 at para. 49.

government policy on the heels of the Hoskins report moving from tacit acceptance to active subsidization of high prices for Rare Disease drugs raises further questions about which small populations are having their medical needs met, and which are not. If the goal were to meet the medical needs of small underserved populations in Canada, addressing barriers to Essential Medicines for Neglected Diseases would be a comparative bargain; the annual cost of eculizumab for a single patient could potentially cover the costs of bringing a drug like albendazole to market in Canada, plus the cost of treating every patient who requires it in Canada for years to come.

So why might Canada – like governments in other HICs – be susceptible to paying high prices for drugs for Rare Diseases in the first place? How has a policy to effectively subsidize expensive drugs been prioritized alongside – and indeed in the 2021 budget prioritized over – national pharmacare, while formal access to notably cheaper Essential Medicines for Neglected Diseases gets almost no attention? One key component is that there is considerable domestic political pressure in HICs to cover Rare Diseases; indeed, Rare Disease stakeholders have been remarkably effective in drawing attention to their concerns.¹¹⁴⁹ This level of pressure does not exist for Neglected Diseases in Canada. There are a number of reasons for this, even outside the financial incentives for the companies selling expensive drugs to lobby for their coverage. One factor influencing disparate political attention to these two sets of uncommon afflictions is the traits of the diseases themselves. Broadly speaking, it's easier to form an activist community around patients with genetic conditions that must be managed for a lifetime rather than infections that can often – if treated – be cured fairly quickly.¹¹⁵⁰ A patient living with a permanent condition, or their caregivers – or even more formidably, a group of patients and/or caregivers with a shared group identity centred on that condition – may be better positioned, and better motivated, to undertake coordinated advocacy against

¹¹⁴⁹ Dunkle, Mary, Wayne Pines & Peter L Saltonstall, "Advocacy groups and their role in rare diseases research" (2010) 686 *Adv Exp Med Biol* 515–525.

¹¹⁵⁰ This is a generalization. It should be acknowledged that some Neglected Diseases do require longer treatment. Treatment for drug-resistant TB can take years rather than months, while some neglected parasitic infections such as strongyloidiasis can require years, or even permanent access to treatment. At the same time, some Rare Diseases may be curable.

barriers to accessing treatment. Even within the context of infectious disease, the permanent nature (and associated community identity) of HIV has been contrasted with the transience of TB as one reason for the far greater advocacy community that has historically built up around HIV, even though the two diseases often affect the same communities, and even the same patient.¹¹⁵¹ Rare disease advocacy groups have in turn found common cause with the pharmaceutical industry to convince governments to pay for expensive drugs.¹¹⁵² Taking this connection further, Rare Diseases have on occasion been targets of so-called astroturf (a term used pejoratively as a contrast to grassroots) patient movements, which are patient organizations created or driven primarily by industry interests rather than organically by patients; Canada has not been immune to this phenomenon, or to the broader influence of pharmaceutical industry funding of pre-existing patient groups.¹¹⁵³ The same cannot really be said for Neglected Diseases; there is no similar attraction for corporate interests to underwrite patient advocacy for, say, albendazole in Canada.¹¹⁵⁴

Another factor is simple demographics; middle-class Canadians coveted by political parties are not the most likely group to contract any of the Neglected

¹¹⁵¹ This example is particularly striking given the frequency of co-infection. Harrington, Mark, "From HIV to Tuberculosis and Back Again: A Tale of Activism in 2 Pandemics" (2010) 50:s3 Clin Infect Dis S260–S266, online: <<https://academic.oup.com/cid/article-lookup/doi/10.1086/651500>>. It should be noted that TB advocacy has been growing over the past decade, however; see e.g., DeLuca, Andrea et al., "The evolving role of advocacy in tuberculosis" (2014) 2:4 The Lancet Respiratory Medicine 258–259, online: <<https://linkinghub.elsevier.com/retrieve/pii/S2213260014700359>>.

¹¹⁵² See e.g., Hemphill, Thomas A, "Extraordinary Pricing of Orphan Drugs: Is it a Socially Responsible Strategy for the U.S. Pharmaceutical Industry?" (2010) 94:2 J Bus Ethics 225–242, online: <<http://link.springer.com/10.1007/s10551-009-0259-x>>. For an example of developing relationships with patients and advocacy groups being suggested as a proper business strategy for Rare Disease drugs, see Ascher, Jan et al., "How to successfully launch a rare disease drug in a patient-centric world", (9 January 2017), *McKinsey & Company - Our Insights*, online: <<https://www.mckinsey.com/industries/life-sciences/our-insights/how-to-successfully-launch-a-rare-disease-drug-in-a-patient-centric-world>>.

¹¹⁵³ See e.g., Goomansingh, Crystal, "Patient groups fighting for coverage of pricey drugs get pharma funding", *Global News* (24 November 2014), online: <<https://globalnews.ca/news/1690509/what-role-do-pharmaceutical-companies-play-in-gaining-support-for-their-drugs/>>; Rose, Susannah L et al., "Patient Advocacy Organizations, Industry Funding, and Conflicts of Interest" (2017) 177:3 JAMA Intern Med 344, online: <<http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2016.8443>>.

¹¹⁵⁴ Politicized pushes for unproven repurposing of drugs like hydroxychloroquine and ivermectin for COVID-19 do not really fit in this category, not least because they have not generally been supported by the pharmaceutical industry.

Diseases discussed herein, but broadly speaking are as susceptible as anyone else to the luck of the genetic draw.¹¹⁵⁵ This matters to a government that boasted, at least temporarily, a Minister of Middle Class Prosperity.¹¹⁵⁶ Meanwhile, marginalized populations disproportionately affected by Neglected Diseases, such as migrant and Indigenous communities, may lack access to the same resources or contacts, may face additional barriers to advocating effectively with decision makers, or may simply have higher political priorities than the niche issue of unmarketed drugs for Neglected Diseases. This is not unique to Canada; similar patterns have been observed internationally in relation to Rare Diseases, striking an intriguing juxtaposition with the emergence of broader access to medicines movements worldwide. The Rare Diseases advocacy movement emerged in the early 1980s, primarily in wealthy Western countries, at roughly the same time that broad-based international NGO coalitions like Health Action International first appeared and began to advocate on issues of access to Essential Medicines.¹¹⁵⁷ Since then, in contrast to Essential Medicines Lists, which were widely adopted by LMICs early on but were not given the same priority by many HICs, the reverse has been true for Rare Diseases. Only in the last decade have Rare Disease laws and policies really begun to emerge in LMICs, and then still largely as a lower priority.¹¹⁵⁸

Rare Diseases possess still further demographic advantages lending themselves to public attention and advocacy in high-income countries. Consider this description from the recent Government of Canada discussion paper on high-cost drugs for Rare Diseases:

¹¹⁵⁵ For sake of argument, a certain level of financial comfort lending itself to tropical vacations could create its own set of risk factors, as the previously discussed case of hookworm in vacationers to the Dominican Republic can attest. However, there's little evidence that this is a primary driver of infection; by contrast, the fact such a case received far more media attention than the issue of refugee claimants requiring the same anti-parasitic drug further illustrates which voices are heard in the press.

¹¹⁵⁶ From 2019 until 2021.

¹¹⁵⁷ Stolk, Pieter, Marjolein J C Willemsen & Hubert G M Leufkens. "Rare essentials: drugs for rare diseases as essential medicines" (2006) 84:9 Bull World Health Organ 745–751.

¹¹⁵⁸ See e.g., Chan, Adrienne YL et al., "Access and Unmet Needs of Orphan Drugs in 194 Countries and 6 Areas: A Global Policy Review With Content Analysis" (2020) 23:12 Value in Health 1580–1591, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1098301520344132>>.

Every so often you hear a personal story, or see an item on the news, about someone living with a rare disease. The patient in the story is often a child, even an infant, but people can be affected at any age. The disease itself is unfamiliar to most people, although the story is not: there is a drug that might save the patient's life or dramatically improve its quality, but it costs hundreds of thousands of dollars, sometimes millions, and is not covered by health insurance. The family can't afford it.¹¹⁵⁹

Genetic disorders, by their very nature, will frequently affect children, a demographic that lends itself to heartwarming personal interest stories (and highly motivated parents). Such stories about cute kids with Rare Diseases treatable only with unfunded or entirely unmarketed drugs are relatively easy to find in the Canadian media; a similarly patient-focused story on a Neglected Disease like Chagas or MDR-TB is comparatively rare. These deficiencies in both government and media attention in turn reinforce each other, leaving Neglected Diseases neglected. Differences in how these narratives unfold are further illustrated in a recent instance where these two classes of diseases were conflated. The story of a child who consumed raccoon feces, drawing rare cute kid attention to albendazole access, has already been recounted.¹¹⁶⁰ That story was in turn promptly repurposed by a national newspaper columnist in the context of Rare Disease advocacy against proposed reforms to the PMPRB; rather than serve to draw attention to broader deficiencies in how medicines are formally approved in Canada, the lack of access to this decades-old off-patent Essential Medicine was

¹¹⁵⁹ Health Canada, *Building a National Strategy for High-Cost Drugs for Rare Diseases* (2021), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/health-related-consultation/National-Strategy-High-Cost-Drugs-eng.pdf>> at p.4.

¹¹⁶⁰ Kost, Hannah, "With clock ticking, doctors, pharmacists come to the rescue after 1-year-old eats raccoon feces", *CBC News* (19 June 2021), online: <<https://www.cbc.ca/news/canada/calgary/raccoon-feces-roundworm-albendazole-1.6069633>>.

misleadingly used as a scare tactic to suggest what might happen if the government lowered prices on expensive new patented drugs for Rare Diseases.¹¹⁶¹

The SAP and Rare Diseases

While none of these reasons can be pinned down as definitive, the fact remains that Rare Diseases have attained a higher political profile than Neglected Diseases in Canada. This unfortunately comes at the expense of identifying broader systemic issues that affect them both. As a prime example, the emphasis on high-priced drugs for Rare Diseases tends to overshadow a wider issue the reader is by now familiar with: whether the drug is formally available at all. In the absence of formal market approval, Rare Disease treatment has historically also been dependent on the SAP. This should be an obvious area of common ground. Somewhat counterintuitively, however, recourse to the SAP has also been used to leverage novel drugs for Rare Diseases against off-patent Essential Medicines. For instance, McMillan and Campbell have argued that “the Special Access Programme is an ineffective pathway for accessing newer, costly drugs” for Rare Diseases while making the dubious claim – at least where Neglected Diseases are concerned – that the SAP “has worked well for cheaper, generic medications in cases where industry has not sought approval to the smaller Canadian market”.¹¹⁶² Unsurprisingly, they cite no evidence for this latter assertion.

Truth be told, in many respects the SAP actually remains more appropriate for the newer Rare Disease drugs touted by McMillan and Campbell than for off-patent Essential Medicines. After all, the SAP is governed by regulations appearing under the heading “Sale of New Drug for Emergency Treatment”. While some are indeed breakthroughs, novel Rare Disease drugs are, by their very nature, drugs for which practitioners cannot draw upon decades of widespread clinical use. This is compounded by the fact that in many jurisdictions novel Rare Disease drugs are

¹¹⁶¹ Maddeaux, Sabrina, “Sabrina Maddeaux: How Canada’s rigid health-care system nearly failed toddler who ate raccoon feces”, *The National Post* (28 June 2021), online: <<https://nationalpost.com/opinion/sabrina-maddeaux-why-canadas-rigid-health-care-system-nearly-failed-toddler-who-ate-raccoon-feces>>.

¹¹⁶² McMillan, Hugh J & Craig Campbell. “We need a ‘made in Canada’ orphan drug framework” (2017) 189:41 CMAJ E1274–E1275, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.170195>>.

more likely than drugs for larger populations to be approved via means such as intermediate biomarkers rather than results in large-scale clinical trials.¹¹⁶³ While such measures have been justified as necessary given the additional challenges of conducting clinical trials on diseases that affect only a small number of people worldwide, the fact remains that these drugs are often less well understood as a result, meaning the goals of ensuring safety and efficacy are not so clearly met even where the drug has been formally approved. As outlined earlier, for established Essential Medicines used around the world for decades – and sometimes previously approved in Canada – safety and efficacy questions are generally easier to answer. That said, squabbling over who is better suited to the SAP is ultimately a distraction from a shared problem. After all, many of the arguments put forward by McMillan and Campbell would fit easily into other sections of this thesis. For instance, one concern they express is that the SAP has led to complacency, where drugs are available to a limited extent, but not as available as they would be if they were formally marketed.¹¹⁶⁴ Given some regularly used drugs for Neglected Diseases have been left in regulatory limbo for decades, this certainly appears to be the case.

In addition to creating access barriers much like those already described for Neglected Diseases, the SAP has similarly been used in the past as a justification for why broader legal and policy reforms are not necessary for Rare Diseases. Such was the case in 1997, when the idea of a Canadian Orphan Drug policy was rejected by Health Canada on the grounds that Canadians with Rare Diseases could take advantage of Orphan Drugs developed elsewhere thanks to “the ability to access treatments that are not approved in Canada via the Special Access Program (SAP)”.¹¹⁶⁵ Contrastingly, in 2012, during a period where a Canadian Orphan Drug policy looked to be on the horizon, taking Rare Disease treatments out of the SAP

¹¹⁶³ This issue is beyond the scope of this thesis, but see e.g., Bax, Bridget E, “Biomarkers in Rare Diseases” (2021) 22:2 *Int J Mol Sci*.

¹¹⁶⁴ McMillan, Hugh J & Craig Campbell. “We need a ‘made in Canada’ orphan drug framework” (2017) 189:41 *CMAJ* E1274–E1275, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.170195>>.

¹¹⁶⁵ Harris, Emily. “Addressing the needs of Canadians with rare diseases: an evaluation of orphan drug incentives” (2018) 5:3 *Journal of Law and the Biosciences* 648–681, online: <<https://academic.oup.com/jlb/article/5/3/648/5088948>> at p.652.

became an explicit selling point of the government's proposal. Per the press release at the time:

Today, when an orphan drug is not available in Canada, the patient's doctor can apply individually for each patient through Health Canada's Special Access Programme. While facilitating access - the current approach also represents a significant burden to the healthcare system. A regulatory framework designed and used specifically to approve drugs to treat small, vulnerable populations will more effectively address this need.¹¹⁶⁶

On its surface, this proposal could – and ideally should – have applied equally to Essential Medicines for Neglected Diseases, provided someone thought to include them under the Orphan Drug umbrella. The opportunity for clarification never arose, however, as this particular announcement never actually manifested in further policy or legislation.¹¹⁶⁷ As will be seen later on, the question of Neglected Diseases and Orphan Drugs is one that other jurisdictions have grappled with as well.

Old drugs for Rare Diseases

While novel drugs have often been the focus of Rare Disease policies, the focus of this thesis is not on new drugs, but on those have been in use for a long time. Here, there are further key parallels between Rare Diseases and Neglected Diseases that point away from enacting policies tailored to Rare Diseases – and especially those focused on pricey novel drugs for Rare Diseases – toward broader reform of the pharmaceutical regulatory system that would help ensure that small, overlooked populations get access to existing drugs. When Harris writes that “while it would

¹¹⁶⁶ “Harper Government Takes Action to Help Canadians with Rare Diseases - Launch of First Ever Canadian Framework to Increase Access to New Treatments and Information and Orphanet” News Release (2012).

¹¹⁶⁷ See e.g., Gibson, Shannon & Barbara von Tigerstrom. “Orphan drug incentives in the pharmacogenomic context: policy responses in the US and Canada” (2015) 2:2 J Law Biosci 263–291.

likely be ideal from a public policy perspective if Canadian companies would invest in more R&D for Orphan Drugs, encouraging companies to launch Orphan Drugs in Canada is a matter of greater importance and urgency”, she is focusing on Rare Diseases, but her comments could just as easily apply to Neglected Diseases.¹¹⁶⁸ The parallels remain – simply read-in Neglected Diseases for Rare Diseases as appropriate – as she expands upon this idea:

While pharmaceutical incentives will not address the issues that patients with rare diseases initially encounter (such as misdiagnosis), policy measures that minimize other disadvantages that patients with rare diseases face (i.e. problems with timely access to appropriate treatment) aligns with the value of equality. Canadian orphan drug incentives should be designed primarily to motivate drug companies to seek Health Canada approval for their orphan drugs. This should be the primary objective because it more directly supports the ultimate goal of providing patients with access to the drugs they need, and because it is likely to have a greater impact than attempts to encourage innovative drug development for rare diseases.¹¹⁶⁹

As this suggests, the key policy objective should be less about encouraging the development of novel Orphan Drugs than ensuring treatments that have already been developed elsewhere come to the Canadian market, whether for Rare Diseases or Neglected Diseases. In turn, focusing only on novel drugs for Rare Diseases is a distraction that does as great a disservice to many Rare Disease patients as it does to Neglected Disease patients. It should be recalled – including, it must be said, by numerous activists, scholars and politicians supporting interventions targeting Rare Diseases – that many Rare Diseases are treated with

¹¹⁶⁸ Harris, Emily. “Addressing the needs of Canadians with rare diseases: an evaluation of orphan drug incentives” (2018) 5:3 Journal of Law and the Biosciences 648–681, online: <<https://academic.oup.com/jlb/article/5/3/648/5088948>>.

¹¹⁶⁹ Harris, Emily. “Addressing the needs of Canadians with rare diseases: an evaluation of orphan drug incentives” (2018) 5:3 Journal of Law and the Biosciences 648–681, online: <<https://academic.oup.com/jlb/article/5/3/648/5088948>>.

old, off-patent medicines; in turn, these off-patent medicines for small but vital markets are vulnerable to the same problems as for Neglected Diseases. Lest we forget, before pyrimethamine, Martin Shkreli cut his teeth on tiopronin, a treatment for the Rare Disease cystinuria.¹¹⁷⁰ Such vulnerabilities can implicate both drugs unmarketed in Canada, and longstanding drugs that belatedly do formally enter the Canadian market.¹¹⁷¹

As an example of the former, consider two key drugs used for the treatment of Wilson's disease, a genetic condition which causes excess copper to build up in the body.¹¹⁷² These two drugs, already raised briefly in the context of American off-patent trolling, have had very different regulatory histories in Canada. One of them, penicillamine, has been approved for sale in Canada since 1964. It has also been on the WHO MEML since 1979 as an antidote to heavy metal poisoning; its role as a "chelator used primarily in Wilson disease" was explicitly recognized by the WHO Expert Committee on Essential Medicines a decade ago.¹¹⁷³ The other, trientine (sold under the tradename Syprine), has been off patent since the early 1990s, but was never submitted for Canadian approval. As a result, the latter could for years only be obtained through the SAP. Then, as Roberts and colleagues relate, a familiar story, involving some familiar players, unfolded:

In 2010, the pharmaceutical company Valeant purchased Aton Pharma, which had previously acquired the US licence for Syprine from Merck and was the current supplier for Health Canada's Special Access Programme, and began to increase the price in the US. Around November 2013,

¹¹⁷⁰ Discussed elsewhere in this thesis. Ramsey, Lydia, "The CEO who jacked up the price of a drug by 5,000% has done this before", *Business Insider* (23 September 2015), online: <<https://www.businessinsider.com/martin-shkreli-history-of-price-hikes-2015-9>>.

¹¹⁷¹ For a good exploration of access to Rare Disease drugs via the SAP, see Blais, Catherine-Marie, *Evaluating Health Policy and Legal Responses: How to Reduce Barriers and Improve Access to Orphan Drugs for Rare Diseases in Canada* (LL.M, Université de Sherbrooke, 2016), online: <https://savoirs.usherbrooke.ca/bitstream/handle/11143/9592/Blais_Catherine_Marie_LLM_2016.pdf>.

¹¹⁷² Also referred to, depending on the source, as Wilson disease.

¹¹⁷³ WHO Expert Committee on the Selection and Use of Essential Medicines, *The selection and use of essential medicines : report of the WHO Expert Committee, March 2011 (including the 17th WHO model list of essential medicines and the 3rd WHO model list of essential medicines for children)* WHO technical report series 965 (Geneva, 2012).

Valeant Canada announced that, as of January 2014, the price of Syprine [obtained through the SAP] would match the US price: roughly Can\$13 244 per month (\$158 928 per year), which is about 13 times the previous price.¹¹⁷⁴

Given that inconsistencies in provincial coverage for this unmarketed drug already left many patients paying out of pocket, the price hike “thus presented immediate and possibly life-threatening difficulties for the about 40 Canadian patients with Wilson disease known to require trientine”.¹¹⁷⁵ Another academic commentary responding to Valeant’s actions concluded that “[i]n effect, trientine is no longer available in Canada”.¹¹⁷⁶ Just as with cycloserine, a foreign price hike disrupted the precarious pathway that made an important unmarketed drug informally available in Canada. Disturbingly, in the United States, Valeant also acquired the rights to penicillamine, thus cornering the market for drugs for Wilson’s Disease and giving it further leverage for exploitive pricing; by 2016, this decades-old drug was ranked one of the most expensive in the United States.¹¹⁷⁷ In Canada, however, the rights to penicillamine were not held by Valeant, and similar off-patent trolling was avoided, leaving only trientine as the focus of concern.

Intriguingly, in this instance, the Canadian government got actively involved in measures to mitigate the issue. An alternative source of trientine was identified and made accessible under the SAP; Roberts and colleagues indicate the PMPRB was one of the parties involved in identifying this alternate source, along with

¹¹⁷⁴ Roberts, Eve A, Matthew Herder & Aidan Hollis. “Fair pricing of ‘old’ orphan drugs: considerations for Canada’s orphan drug policy” (2015) 187:6 CMAJ 422–425, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.140308>>.

¹¹⁷⁵ Roberts, Eve A, Matthew Herder & Aidan Hollis. “Fair pricing of ‘old’ orphan drugs: considerations for Canada’s orphan drug policy” (2015) 187:6 CMAJ 422–425, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.140308>>.

¹¹⁷⁶ Chandok, Natasha & Eve A Roberts, “The Trientine Crisis in Canada: A Call to Advocacy” (2014) 28:4 Canadian Journal of Gastroenterology and Hepatology 184–184, online: <<http://www.hindawi.com/journals/cjgh/2014/672809/>>.

¹¹⁷⁷ Ramsey Pflanzner, Lydia, “The 10 most expensive drugs in the US”, *Business Insider* (30 September 2016), online: <<https://www.businessinsider.com/most-expensive-drugs-in-america-2016-9#cuprimine-penicillamine-valeant-39800-3>>;

See also: United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System* (United States Senate, 2016).

physicians and patient groups.¹¹⁷⁸ This action by the PMPRB underscores another longstanding failing of the SAP: that it has placed the burden of identifying sources on the individual physician, who is generally in a notably worse position to do so than would be a government body whose *raison d'être* is regulating access to unapproved drugs. As Roberts *et al.* emphasize, “Patients, disease-focused nongovernmental organizations, and physicians do not have the expertise or the capacity to scour world markets” while insured patients “may have no incentive to do so”.¹¹⁷⁹ Here again the parallels with Neglected Diseases shine through.

As part of addressing this broader issue, Roberts and colleagues propose that the PMPRB’s existing data collection program could be extended “to unpatented drug pricing for all products that are sole-sourced in Canada”.¹¹⁸⁰ In turn, “where the Canadian price proves excessive, relative to prices in all other markets, the board could generate the information required for assisting patients, clinicians and insurers to identify competitive suppliers”.¹¹⁸¹ “This would not”, they suggest, “be outside the current activities of the Patented Medicine Prices Review Board, which, despite its name, also periodically monitors generic drug prices”.¹¹⁸² This is an interesting proposal, with similarities to the list of important drugs with single suppliers once mooted by HESA.¹¹⁸³ Furthermore, the PMPRB already

¹¹⁷⁸ Roberts, Eve A, Matthew Herder & Aidan Hollis. “Fair pricing of ‘old’ orphan drugs: considerations for Canada’s orphan drug policy” (2015) 187:6 CMAJ 422–425, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.140308>>.

¹¹⁷⁹ Roberts, Eve A, Matthew Herder & Aidan Hollis. “Fair pricing of ‘old’ orphan drugs: considerations for Canada’s orphan drug policy” (2015) 187:6 CMAJ 422–425, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.140308>>. That said, the capacity of effective NGOs and patient groups probably should not be dismissed.

¹¹⁸⁰ Roberts, Eve A, Matthew Herder & Aidan Hollis. “Fair pricing of ‘old’ orphan drugs: considerations for Canada’s orphan drug policy” (2015) 187:6 CMAJ 422–425, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.140308>>.

¹¹⁸¹ Roberts, Eve A, Matthew Herder & Aidan Hollis. “Fair pricing of ‘old’ orphan drugs: considerations for Canada’s orphan drug policy” (2015) 187:6 CMAJ 422–425, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.140308>>.

¹¹⁸² Roberts, Eve A, Matthew Herder & Aidan Hollis. “Fair pricing of ‘old’ orphan drugs: considerations for Canada’s orphan drug policy” (2015) 187:6 CMAJ 422–425, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.140308>>.

¹¹⁸³ Standing Committee on Health. *Drug Supply in Canada: A Multi-Stakeholder Responsibility*, 41st Parliament, 1st Session (2012) at p.13. This list is also akin to the drugs identified by the US FDA as “medically necessary”. Center for Drug Evaluation and Research, *Drug Shortage Management*, Manual of Policies and Procedures MAPP 4190.1 Rev. 3 (US FDA, 2018) at p.14.

asserts jurisdiction over unmarketed patented medicines obtained via the SAP.¹¹⁸⁴ As a bonus, provided that an alternate source for an unmarketed off-patent drug is actually available, neither patents nor domestic market approval shield the existing sole source. An example of how this might play out in practice was seen earlier in this thesis in the case of parenteral artesunate, where Canadian access via the SAP has away shifted from an American source whose price recently skyrocketed towards a cheaper WHO Prequalified source.¹¹⁸⁵ As such, extending the PMPRB's price reviews to alternate sources of unmarketed off-patent medicines seems a reasonable step to take, even at a moment when the PMPRB may be hesitant to stretch its wings in the wake of the Federal Court of Appeal's rebuke of expansive interpretations of its mandate in *Alexion*.¹¹⁸⁶

The information thus gleaned would be valuable not only for finding alternative sources of high-priced drugs, but also for offering a clearer landscape for that subset of drugs that are currently unmarketed in Canada but provided to patients for free by the manufacturer under the SAP.¹¹⁸⁷ This is important, because as Rare Diseases will serve to underscore momentarily, market entry alone is no panacea. Indeed, in some cases it can actually exacerbate access problems, particularly around cost, whether that cost is shouldered by the patient or the state. The issue of cost for a drug previously provided *gratis* via the SAP has already been raised with the relatively mild example of ivermectin.¹¹⁸⁸ This means it is important to plan ahead. While Canada has thus far been spared any direct off-patent trolling, even as trolled American prices were exported via the SAP and, in

¹¹⁸⁴ As affirmed by the SCC in *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 (CanLII), online: <<https://canlii.ca/t/2fbv3>>. This issue is explored elsewhere in this thesis.

¹¹⁸⁵ As discussed, the Canadian Malaria Network now draws upon the cheaper Chinese source Guilin. Canadian Malaria Network, "Introduction to the Canadian Malaria Network" (April 2019), online: <https://src.healthpei.ca/sites/src.healthpei.ca/files/Laboratory%20Services/CMN_Complete_Malaria_Package.pdf>.

¹¹⁸⁶ *Alexion Pharmaceuticals Inc. v. Canada (Attorney General)*, 2021 FCA 157.

¹¹⁸⁷ This is true not only of certain Neglected Disease drugs, but also some rare disease drugs, often provided under company "compassionate access" provisions.

¹¹⁸⁸ Boggild, Andrea & Antoine Corbeil. "Hot topics in tropical medicine: Approval of Ivermectin by Health Canada", (12 April 2019), online: *BMC Blog Network - On Medicine* <<https://blogs.biomedcentral.com/on-medicine/2019/04/12/hot-topics-tropical-medicine-approval-ivermectin-health-canada/>>.

some cases, were masterminded from Valeant's headquarters in Laval, recent events involving the drug cysteamine, used to treat the rare genetic disorder cystinosis, had a similar impact on Canadian prices and further underscore both the fragility of Canada relying upon access to a foreign source of an unmarketed medicine for decades, and the failures of the SAP.

Cysteamine and the SAP

As Rare Diseases go, cystinosis – characterized by the accumulation of the amino acid cystine in cells, ultimately leading to symptoms including kidney failure and blindness – boasts the interesting attribute of being notably less rare in Québec than elsewhere in the world, ultimately making Québec one of the most promising commercial markets for this particular Rare Disease.¹¹⁸⁹ Examined for other conditions like radiation sickness in the 1950s, cysteamine was recognized as a possible cystinosis treatment in 1976.¹¹⁹⁰ It has been marketed for treatment of cystinosis in the US under the tradename Cystagon since 1994, but Cystagon has never been approved in Canada; as such, for more than two decades, Canadian patients obtained it via the SAP.¹¹⁹¹ That patients receiving the drug have to take it multiple times a day for life indicates yet again how the short term, emergency nature of the SAP, including its requirement of a new request every few months, has been a poor fit for long-term, or indeed permanent, access.

However, in 2017, Health Canada approved a new delayed-release formulation of cysteamine produced by Horizon Pharma under the tradename Procysbi. This was the first cysteamine product ever formally marketed in Canada. Despite containing the same active drug, Procysbi came with a price tag of

¹¹⁸⁹ De Braekeleer, Marc, "Hereditary Disorders in Saguenay-Lac-St-Jean (Quebec, Canada)" (1991) 41:3 Hum Hered 141–146, online: <<https://www.karger.com/Article/FullText/153992>>.

¹¹⁹⁰ Besouw, Martine et al., "Cysteamine: an old drug with new potential" (2013) 18:15–16 Drug Discovery Today 785–792, online: <<https://linkinghub.elsevier.com/retrieve/pii/S135964461300038X>>.

¹¹⁹¹ Standing Committee on Health, Canadians affected by rare diseases and disorders: Improving access to treatment, 42nd Parliament, 1st Session (2019), online: <<https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf>> at p.14.

\$325,000 per year, versus \$5,000 per year for Cystagon obtained via the SAP.¹¹⁹² While a delayed release formulation might conceivably confer some patient benefit, it is nearly impossible to conceive how that benefit could be worth an additional \$320,000 per year. Accordingly, a review of Procysbi by the CADTH Canadian Drug Expert Committee concluded that even “at a price reduction of 95%, the ICUR [Incremental Cost-Utility Ratio] remains greater than \$100,000 per QALY [Quality-Adjusted Life Year] compared with no treatment”.¹¹⁹³ One need not be a health economist to ascertain that this is not a particularly impressive result. Given such a mismatch, the PMPRB filed a Statement of Allegations against the makers of Procysbi in 2019, alleging excessive pricing.¹¹⁹⁴ It is important to note that in doing so the PMPRB draws key comparisons between an approved drug, Procysbi, and an unapproved drug available only via the SAP, Cystagon:

Procysbi and Cystagon both contain the same single medicinal ingredient (cysteamine bitartrate). In addition, the mechanism of action for both Procysbi and Cystagon is identical. Both Procysbi and Cystagon deplete the cystine that accumulates and crystallizes in the tissues of the body, as a result of nephropathic cystinosis. Moreover,

¹¹⁹² Patented Medicine Prices Review Board, *Patented Medicine Prices Review Board in the Matter of the Patent Act, R.S.C., 1985, c. P-4, as amended and in the Matter of Horizon Pharma (the “Respondent”) and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name Procysbi Statement of Allegations of Board Staff*, by Patented Medicine Prices Review Board (2019), online: <<http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1423>>.

¹¹⁹³ CADTH, *Pharmacoeconomic Review Report: Cysteamine delayed-release capsules (Procysbi): Horizon Pharma Ireland Ltd. Indication: For the treatment of nephropathic cystinosis*, CADTH Common Drug Reviews (Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, 2018).

¹¹⁹⁴ Patented Medicine Prices Review Board, *Patented Medicine Prices Review Board in the Matter of the Patent Act, R.S.C., 1985, c. P-4, as amended and in the Matter of Horizon Pharma (the “Respondent”) and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name Procysbi Statement of Allegations of Board Staff* (2019), online: <<http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1423>>. It should be noted that the PMPRB had jurisdiction in this case because new patents affected an old drug, even though the underlying drug itself remained unchanged. Per the subsequent PMPRB complaint, this formulation involved two patents: a) Canadian Patent No. CA2640531, entitled “Enterically coated cysteamine, cystamine and derivatives thereof,” issued January 3, 2017; b) Canadian Patent No. CA2914770, entitled “Delayed release cysteamine bead formulation, and methods of making and using same,” issued September 27, 2016. This patent would not itself impact access to cysteamine in its older form (i.e., in the Cystagon formulation).

the same indications and contraindications exist for both Procysbi and Cystagon, reflecting the fact that they utilize the identical active ingredient. There is no therapeutic advantage between Procysbi and Cystagon: neither is inferior to the other in terms of the efficacy of treatment, and both lead to the same therapeutic outcome. In the United States, Procysbi was approved under a 505(b)(2) regulatory pathway that relied upon the safety and effectiveness of Cystagon (NDA 020392) as a reference listed drug.¹¹⁹⁵

In drawing this equivalence, the PMPRB is chipping away at the ongoing legal fictions that underpin Canada's repeated assertions that use of a drug via the SAP cannot be used to establish a record of safety and efficacy.¹¹⁹⁶ As the CADTH review suggests, current evidence indicates that Cystagon, obtained for decades via the SAP, is as safe and effective as the officially marketed Procysbi, and available at a fraction of the cost. Siding with the officially marketed version of the drug in this instance might be in the interests of encouraging formal Health Canada approval, but would also actively go against the interests of the patient (particularly given differences in drug coverage across the country), without offering any real advances in relation to the underlying regulatory goals of safety, efficacy and quality.

As of this writing, this PMPRB case is still in progress. In the interim, however, the approval of Procysbi erected new barriers to accessing the far less expensive Cystagon. If a product is marketed and available in Canada, the equivalent product cannot be accessed via the SAP; thus, Health Canada initially cancelled SAP requests for Cystagon.¹¹⁹⁷ Fortunately for patients in this particular

¹¹⁹⁵ Patented Medicine Prices Review Board, *Patented Medicine Prices Review Board in the Matter of the Patent Act, R.S.C., 1985, c. P-4, as amended and in the Matter of Horizon Pharma (the "Respondent") and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name Procysbi Statement of Allegations of Board Staff* (2019), online: <<http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1423>>. At para 8.

¹¹⁹⁶ This issue will be explored in depth later in this thesis.

¹¹⁹⁷ Standing Committee on Health, *Canadians affected by rare diseases and disorders: Improving access to treatment*, 42nd Parliament, 1st Session (2019), online:

instance, the story does not quite end there; following concerns about the price, physicians who had requested Cystagon were contacted by the SAP itself, inviting them to resubmit and asking them to provide medical rationale for why their patient required the unapproved Cystagon rather than the approved Procysbi.¹¹⁹⁸ Here again, the result is simultaneously something of both a legal and a medical fiction; nevertheless, in material provided to HESA for its examination of Rare Diseases, the Minister of Health noted that following this change, more than 60 patients had been granted access to Cystagon via the SAP after Procysbi's approval.¹¹⁹⁹ Thus, the rules of the SAP were bent not merely to sustain decades of access to an old, unapproved drug reliant on a mechanism designed for emergency access to new drugs, but to do so in direct competition with a vastly more expensive, Health Canada-approved version of the same drug. This highlights once again the cracks in the veneer of the SAP.

Of course, all this would have been avoided if Cystagon had been formally available in Canada in the first place. This did not go unnoticed when the issue was examined by HESA, where “witnesses articulated that the Cystagon case highlights the need for Health Canada to develop incentives for drug manufacturers who provide drugs through the SAP to apply for market authorization in Canada through the standard regulatory approval process”.¹²⁰⁰ Here it must be emphasized yet again that the drug being obtained via the SAP was not a novel drug that required special access in the short term pending imminent Canadian approval, but one in use in Canada for decades without any application for approval prior to

<<https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf>> at p.15.

¹¹⁹⁸ Standing Committee on Health, Canadians affected by rare diseases and disorders: Improving access to treatment, 42nd Parliament, 1st Session (2019), online: <<https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf>> at p.15.

¹¹⁹⁹ Standing Committee on Health, Canadians affected by rare diseases and disorders: Improving access to treatment, 42nd Parliament, 1st Session (2019), online: <<https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf>> at p.15.

¹²⁰⁰ Standing Committee on Health, Canadians affected by rare diseases and disorders: Improving access to treatment, 42nd Parliament, 1st Session (2019), online: <<https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf>> at p.16.

Procysbi. A system that results in paying 65x the price for a decades-old drug simply because a new manufacturer has the imprimatur of Health Canada is the definition of false economy. Allowing patients to come to harm because they cannot afford the officially sanctioned version of the product at its new price is also an unacceptable outcome. Under such circumstances, access unnecessarily suffers as the result of a regulatory system dependent upon commercial interest, while the regulatory goals of safety, efficacy and quality have not been furthered,

If Procysbi weren't sufficient to make the point about the disjunct between regulation and reality, a second cysteamine product for cystinosis patients, this time in the form of eyedrops, subsequently entered the Canadian market in 2019. This product was not patented in Canada, taking it out of the PMPRB's jurisdiction. Where Procysbi's approval affected access to a different source of the same drug via the SAP, the marketing of this formulation, at a price tag of over \$100,000 per year, prevented patients from receiving their old eyedrops from compounding pharmacies.¹²⁰¹ While the disadvantages of compounding as a systemic solution have been outlined earlier, a six-figure price tag for access to a regulated version of a product must also count as a disadvantage.

Thus, Rare Disease treatments underscore the same lessons seen with Essential Medicines for Neglected Diseases: the existing approach to accessing important but unmarketed old drugs makes little sense. At the same time, it is also worth emphasizing that in the cases of both trientine and cysteamine, government entities took additional steps to address the problem, including identifying a new affordable source via the SAP (trientine) and bending the rules of the SAP itself to preserve access to an existing source (cysteamine). This underscores once again which drugs have attracted greater government attention; however, it also shows how broader systemic changes could benefit both groups of drugs rather than relying on *ad hoc* solutions for individual drugs. Ultimately, for a drug that is the long-established standard of care, the focus should be getting the drug to the

¹²⁰¹ Grant, Kelly, "Nobody can afford this': Family left helpless after Health Canada approves official version of prescription eye drops", *Globe and Mail* (28 August 2019), online: <<https://www.theglobeandmail.com/canada/article-nobody-can-afford-this-family-left-helpless-after-health-canada/>>.

patient, not jumping through regulatory hoops decades after the fact. If such steps can be taken for drugs for Rare Diseases, surely they can be taken for established Essential Medicines for Neglected Diseases.

Regardless of the conditions they treat, once Canada has identified drugs that a) are necessary to provide patients in Canada with the standard of care, and b) are not formally available in Canada, the question becomes how to improve access. Broadly, potential interventions can be separated into two main categories: Improving access to unapproved drugs, and bringing drugs formally to market. As discussed in the next chapter, these two categories impact each other in certain contexts, and are strictly siloed in others. In both instances, the past decade has seen both areas evolve, a process recently accelerated by COVID-19. However, further steps are necessary to maximize the impact of these interventions.

Chapter 11: Developments in access

Emerging mechanisms for access - Extraordinary Use New Drugs (EUNDS)

One relatively recent but often overlooked development in Canada's pharmaceutical regulatory system shows that substantive changes to bring unapproved drugs to market are not only possible, but do not actually require major changes to existing regulatory regimes. This was a 2011 amendment to the *Food and Drug Regulations* to include new provisions for Extraordinary Use New Drugs (EUNDS). EUNDS are an especially niche class of drugs which includes those for purposes like "military medical countermeasures" such as treating inhaled anthrax from a terrorist attack.¹²⁰² As such, an especially salient characteristic of many EUNDS is that they cannot readily go through the traditional approval process – after all, it's tough to run an ethical clinical trial involving biological weapons. The Regulatory Impact Analysis Statement accompanying the amendment described the rationale as follows:

The regulatory framework for new drug submissions works well for most drugs, but there is a group of extraordinary use drugs for which traditional clinical trials cannot be conducted. According to C.08.002(2)(g) and (h) of the Regulations, the manufacturer must demonstrate clinical safety and provide substantial evidence of clinical effectiveness of the drug for the purpose and under the conditions of use recommended. For drugs such as those needed to prevent or treat pandemic influenza or to treat inhaled anthrax from a terrorist attack, there are ethical and/or logistical challenges in designing and conducting clinical trials. A researcher cannot intentionally expose clinical trial subjects to the causative agent in question, and the occurrence of the conditions of use recommended (i.e. pandemic influenza outbreak or anthrax exposure) is unpredictable, sporadic and infrequent, so the standards for

¹²⁰² Food and Drug Regulations - C.R.C., c. 870 (Section C.08.004.01).

clinical safety and effectiveness set out in the Regulations for new drugs cannot be met.¹²⁰³

This amendment addressed a longstanding concern that had also directly implicated the SAP. A 2005 report from the Auditor General of Canada on Canada's emergency preparedness had observed that most medical countermeasures were not licensed for use in Canada, but rather imported from the United States via the SAP. It concluded that "Use of the Special Access Program is inappropriate" for this purpose, and issued the recommendation that "Health Canada should establish an appropriate legal structure for providing unlicensed drugs in an emergency".¹²⁰⁴ The 2011 amendments exceed this recommendation. Rather than simply improving access to unapproved drugs, they smooth the path to formal market approval. They do so by creating a new type of regulatory submission for EUNDS. Doing so does not involve reinventing the regulatory wheel; as the accompanying explanation reads:

The EUND submission requirements differ slightly from those for new drugs, but the structure of the submission and the operational processes within Health Canada remain the same. Special consideration will be given to preclinical and clinical data requirements, labelling and post-market data collection and reporting for EUNDS. This approach allows Health Canada to put into place an appropriate risk-based framework for authorizing EUNDS.¹²⁰⁵

¹²⁰³ "Regulations Amending the Food and Drug Regulations (1319 — New Drugs for Extraordinary Use)," Canada Gazette Part II, Vol. 145, No. 8 (25 March, 2011) online: <<https://canadagazette.gc.ca/rp-pr/p2/2011/2011-04-13/html/sor-dors88-eng.html>>.

¹²⁰⁴ Office of the Auditor General, "National security in Canada: the 2001 Anti-Terrorism Initiative : air transportation security, marine security, and emergency preparedness." (2005) 2005 Report of the Auditor General of Canada at p.26.

¹²⁰⁵ "Regulations Amending the Food and Drug Regulations" (1319 — New Drugs for Extraordinary Use) Canada Gazette Part II, Vol. 145, No. 8 (25 March, 2011) online: <<https://canadagazette.gc.ca/rp-pr/p2/2011/2011-04-13/html/sor-dors88-eng.html>>.

The EUNDS approval framework is both a useful measure to improve access to a specific category of unmarketed drugs by facilitating their approval, and a good example of how such measures can be carried out within the existing system. As such, it should serve as inspiration for further reforms to bring important drugs to market. There is no clear reason why a similar regulatory pathway for Essential Medicines could not be developed, drawing on a similar risk-based framework for a limited class of drugs within the existing system. In fact, adopting existing findings of the WHO Expert Committee on Selection and Use of Essential Medicines, in conjunction with regulatory data from other jurisdictions and evidence underpinning Canadian treatment guidelines, would far exceed the evidentiary bar currently set for EUNDS. A further area in which the EUNDS submission pathway serves as a useful example is that there are no fees for EUNDS applications (at least at the time of this writing).¹²⁰⁶ A decade later, however, while drugs have received approval via the EUNDS pathway, it remains rather low profile, and has not served as a catalyst for broader reforms.¹²⁰⁷ In the interim, another mechanism has been introduced to improve access to unmarketed drugs, this time in response to a particular public health issue in Canada.

Access to Drugs in Exceptional Circumstances (UPHN)

The Access to Drugs in Exceptional Circumstances (UPHN) access pathway came into effect in 2017.¹²⁰⁸ This higher-profile reform to the *Food and Drug Regulations*

¹²⁰⁶ Health Canada, “Guidance Document - Submission and Information Requirements for Extraordinary Use New Drugs (EUNDS)” (28 May 2021), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/submission-information-requirements-extraordinary-drugs-eunds.html>>.

¹²⁰⁷ It has not been completely idle, however. Most importantly, the manufacturer of a smallpox vaccine previously stockpiled via the SAP received approval via the EUNDS pathway. As revisited later, this approval has very recently taken on new significance, as this vaccine is also the only vaccine approved for monkeypox. See Bavarian Nordic A/S, “Health Canada Extends Approval of IMVAMUNE to Immunization against Monkeypox and Orthopox Viruses”, (12 November 2020), online: <<https://www.globenewswire.com/news-release/2020/11/12/2125193/0/en/Health-Canada-Extends-Approval-of-IMVAMUNE-to-Immunization-against-Monkeypox-and-Orthopox-Viruses.html>>. However, one disadvantage of approval of this vaccine via this pathway is of course that the evidence of its efficacy for monkeypox is not based on human trials.

¹²⁰⁸ No official short form for the name of this mechanism seems to have been adopted. UPHN, drawn from Urgent Public Health Need, is adopted here, as it has on occasion been used by the

has served to illustrate the unmet need not only for unmarketed Essential Medicines for Neglected Diseases, but also for better means of accessing them. The UPHN again demonstrates that Canada is capable of taking action to improve access to unmarketed medicines when pressed to do so. Unlike the EUNDS pathway, however, it does not result in formal approval of the drug. Instead, it remains a means of improving temporary access to an unapproved medicine.

The UPHN was created by the “Regulations Amending the Food and Drug Regulations (Importation of Drugs for an Urgent Public Health Need).”¹²⁰⁹ As the “Urgent Public Health Need” label suggests, the UPHN operates at the population level, rather than being tied to specific patients like the SAP. To this end, it permits large-scale importation from approved foreign regulatory authorities. The foreign regulatory authorities permitted under the UPHN are those of the European Union, the United States and Switzerland.¹²¹⁰ The last of these foreign regulatory authorities was included, as will be seen, for a very specific reason. Under the UPHN, the Chief Medical Officer or equivalent of a jurisdiction – which is most commonly a Province or Territory, but can also be another entity such as the federal First Nations and Inuit Health Branch – makes a request to the federal Minister of Health for access to an unmarketed drug.¹²¹¹ If the Minister of Health accepts the request, the drug will be added to the List of Drugs for an Urgent Public Health Need (UPHN List).¹²¹² Once listed, its importation into the named jurisdiction will be permitted for up to one year, without limitations on quantity.¹²¹³

Although the creation of the UPHN was catalyzed by a very specific public health issue, it nonetheless addresses some broader access barriers for unmarketed medicines, at least on a temporary basis. The Regulatory Impact Analysis Statement accompanying the regulations establishing the UPHN explicitly

Government of Canada and is readily distinguishable from the short forms used for other mechanisms.

¹²⁰⁹ “Regulations Amending Food and Drugs Act —Food and Drug Regulations (Importation of Drugs for an Urgent Public Health Need)” *Canada Gazette Part II*, Vol. 151, No. 14 (July 12, 2017).

¹²¹⁰ C.10.001(2)(b), *Food and Drug Regulations* (C.R.C., c. 870).

¹²¹¹ C.10.001(1), *Food and Drug Regulations* (C.R.C., c. 870).

¹²¹² C.10.001(2)(e), *Food and Drug Regulations* (C.R.C., c. 870).

¹²¹³ C.10.001(2)(a), *Food and Drug Regulations* (C.R.C., c. 870).

outlines the drawbacks to other existing access mechanisms that necessitated this pathway:

In Canada, there are currently regulatory pathways that provide access to drugs that are not authorized for sale in Canada. These include Health Canada's Special Access Programme (SAP) and the filing of a Clinical Trial Application (CTA). However, there is no regulatory mechanism available in Canada to address an urgent public health need through a population-based approach. The SAP was designed to address individual patient needs and, therefore, requires an application to be made for the drug by the treating physician. The authorization that is issued is for a specific quantity of drug and must be issued once again if treatment for additional patients is sought. This system works well for the individual patient–practitioner situation, but was never intended for use in a population health treatment context to address a public health emergency such as the current opioid crisis in Canada. Clinical trials are typically designed and conducted for the purpose of studying a drug's effect and are not an efficient means for the ongoing treatment of patients. In addition, the filing of a CTA represents an even greater administrative burden than that of making an application under the SAP.¹²¹⁴

The RIAS thus spells out longstanding problems with existing pathways (despite its dubious assertion that the SAP “works well for the individual patient–practitioner situation”). The RIAS then goes a step further to explicitly recognize the fact that effective treatments may not be authorized in Canada for reasons that “may include a business decision by the manufacturer to not apply for an authorization in Canada because it is a smaller market, or a business decision to seek authorization

¹²¹⁴ “Regulations Amending Food and Drugs Act —Food and Drug Regulations (Importation of Drugs for an Urgent Public Health Need)” *Canada Gazette Part II*, Vol. 151, No. 14 (July 12, 2017).pp.1980.

in Canada at a later date”.¹²¹⁵ These are important points to recognize in the creation of a new access mechanism, even if they are not ultimately addressed by the UPHN. Ultimately, however, the UPHN mechanism does not exist because Canada wanted to tackle broader access concerns for important but unmarketed drugs, but rather as the result of increased government attention to a particular set of access issues faced by another marginalized group whose needs have historically been largely overlooked by Canadian policymakers: people who use illicit drugs. The driving impetus behind the UPHN was what is termed in the RIAS the “opioid crisis” – an increase in deaths via overdose from the use of opioid drugs, driven in particular by the increasing presence of more powerful opioids within the drug supply, most notoriously fentanyl.¹²¹⁶ It is not simply in recognition of its high regulatory standards that Switzerland is one of the three foreign regulatory authorities from which drugs can be imported under the UPHN; Switzerland is the primary source of medical-grade diamorphine (more commonly known by its former tradename, heroin).

The war on drugs is well beyond the scope of this paper; however, it should be acknowledged that, far from being simply an illicit scourge, many opioids are highly useful medicines whose importance is reflected in their inclusion on the WHO MEML. Fentanyl is itself an Essential Medicine; indeed, it was added to the WHO MEML (for management of chronic cancer pain) in 2017, even as the opioid crisis was in the headlines in countries like Canada and the United States. In turn, influencing the implementation of international drug control treaties is another area where Essential Medicines status has had a tangible impact.¹²¹⁷ Domestically,

¹²¹⁵ “Regulations Amending Food and Drugs Act —Food and Drug Regulations (Importation of Drugs for an Urgent Public Health Need)” *Canada Gazette Part II*, Vol. 151, No. 14 (July 12, 2017).pp.1980.

¹²¹⁶ While undeniably a crisis, other terminology, such as “overdose crisis”, is preferred in some circles. However, as noted, opioid crisis is the term used by Canada in relation to UPHN and will thus be used here.

¹²¹⁷ See e.g., Lohman, Diederik & Damon Barrett, “Scheduling medicines as controlled substances: addressing normative and democratic gaps through human rights-based analysis” (2020) 20:1 BMC Int Health Hum Rights 10. Presence on the WHO MEML and on national EMLs has directly influenced the decision-making process around whether certain medicines should be scheduled; see for instance the respective discussions of ketamine and GHB (γ-Hydroxybutyric acid) in World Health Organization, ed, *Thirty-fifth report / WHO Expert Committee on Drug Dependence: Hammamet, Tunisia, 4 - 8 June 2012*, WHO technical report series 973 (Geneva: World Health

one of the very first references to the intuitive concept of “essential medicines” in a Canadian courtroom similarly involved reference to the medical and non-medical uses of a prohibited substance.¹²¹⁸ More recently, controlled substances have had their own history with the SAP. In fact, they are the basis for one of the few changes ever made to the actual regulations underlying the SAP during the initial half century of its existence, rather than mere tweaks to policies built on top. In 2013, the Conservative government banned certain drugs, including heroin, from being accessed via the SAP.¹²¹⁹ The restriction added to the regulations made it clear that the “Minister shall not issue a letter of authorization... for a new drug that is or that contains a restricted drug”.¹²²⁰ This change was made in response to a clinical trial using prescription heroin in Vancouver, following which patients had continued to receive the drug via the SAP; halting this ongoing access via the SAP was a less publicized part of the Harper administration’s opposition to opioid harm reduction, more famously on display in its attempts to shut down the Insite safe injection site in Vancouver.¹²²¹ This change to the SAP was partially reversed – for heroin specifically – in 2016 under the subsequent Trudeau administration.¹²²² By 2022, the restriction was removed completely, expanding accessibility of other controlled

Organization, 2012), and the discussions of ketamine and tramadol in World Health Organization, ed, *Thirty-sixth report / WHO Expert Committee on Drug Dependence: Geneva, Switzerland, 16 - 20 June 2014*, WHO technical report series 991 (Geneva: World Health Organization, 2015).

¹²¹⁸ In a New Brunswick case addressing the prescription of alcohol for medical purposes under temperance legislation, the judge observes that “Intoxicating liquors are declared by medical authorities to be an essential drug, useful in their place like other drugs of pharmacopoeia”. *Rex v. McAllister*, 1913 CanLII 387 (NB QB) (no pinpoint).

¹²¹⁹ Government of Canada, “Heroin and Other Dangerous Drugs Are Banned from Health Canada’s Special Access Programme - Government of Canada Puts Safety and Security of Canadians First and Focuses on Treatment and Recovery” News Release (2013), online: <<https://www.canada.ca/en/news/archive/2013/10/heroin-other-dangerous-drugs-are-banned-from-health-canada-special-access-programme-government-canada-puts-safety-security-canadians-first-focuses-treatment-recovery.html>>.

¹²²⁰ “Regulations Amending Certain Regulations Relating to Access to Restricted Drugs” *Canada Gazette Part II*, Vol. 147, No. 22 (23 October 2013). The restriction was found in C.08.010(1.1) of the *Food and Drug Regulations*.

¹²²¹ The latter issue is famously addressed in *Canada (Attorney General) v. PHS Community Services Society*, 2011 SCC 44, [2011] 3 S.C.R. 134.

¹²²² Woo, Andrea. “Health Canada overturns ban on medical heroin”, *Globe and Mail* (13 May 2016), online: <<https://www.theglobeandmail.com/news/national/health-canada-proposes-to-allow-doctor-requests-to-prescribe-heroin/article30020597>>; “Regulations Amending Certain Regulations Made Under the Controlled Drugs and Substances Act (Access to Diacetylmorphine for Emergency Treatment)” *Canada Gazette Part II*, Vol. 150, No. 22 (7 September, 2016).

substances with actual or potential medical value.¹²²³ Even without such targeted barriers in place, however, expanding harm reduction programs is difficult to do on an individual, identified patient basis; by the time someone at risk of an overdose is identified, it may already be too late. Instead, where the required drugs are not merely restricted but unapproved in Canada, broader programs involving access require a population-level access mechanism like the UPHN.

Although the opioid crisis was the inspiration behind the UPHN, the mechanism was, sensibly, designed to be flexible enough to accommodate other urgent public health needs. A flu pandemic is mentioned as another potential example in the RIAS; the government website on the mechanism offers the third example of a “military health emergency”.¹²²⁴ Nevertheless, the primary inspiration is readily apparent when looking at the initial list of drugs permitted for importation under the UPHN at the time of its launch. As planned, three forms of diamorphine (one injectable and two tablet) were the first three drugs to appear on the UPHN List; the “urgent public health need” was the “opioid crisis”, the notifying jurisdiction was British Columbia (the province hardest hit by the crisis), and their date of notification was June 20, 2017.¹²²⁵ A number of other drugs used in response to the opioid crisis, such as a range of forms of suboxone unavailable in Canada, were also notified by British Columbia on the same day, accounting for nine of ten requests on the initial UPHN List.¹²²⁶

At the bottom of the inaugural UPHN List, however, is one drug not intended to tackle the opioid crisis. It plays no direct role in a flu pandemic or a military health emergency. It is a drug for a condition overlooked in the process of

¹²²³ “Regulations Amending Certain Regulations Relating to Restricted Drugs (Special Access Program): SOR/2021-271” *Canada Gazette Part II*, Vol. 156, No. 1 (5 January 2022). This has impacted the potential clinical use of psychedelics, an emerging topic beyond the scope of this thesis.

¹²²⁴ Health Canada, “Questions and Answers - Access to Drugs in Exceptional Circumstances”, (27 June 2017), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/access-drugs-exceptional-circumstances/drugs-urgent-public-health-need-questions-answers.pdf>>.

¹²²⁵ Health Canada, “List of Drugs for an Urgent Public Health Need”, 6 July 2017 version, in possession of author.

¹²²⁶ Health Canada, “List of Drugs for an Urgent Public Health Need”, 6 July 2017 version, in possession of author.

developing the UPHN, and never mentioned in connection with it in the *Canada Gazette*. This drug, rifapentine, was requested by First Nations and Inuit Health Branch, with a notification date of June 22, 2017. The urgent public health need in question is now explicitly labelled on the UPHN List as the “tuberculosis crisis”. Rifapentine (sold under the tradename Priftin, as noted on the UPHN List) is used to treat latent tuberculosis infection (LTBI); it can play an important role in protecting vulnerable populations, as well as in treating contacts of patients to ward off outbreaks. At the same time, latent TB only becomes harmful if it becomes active TB; most people with latent infection never become sick.¹²²⁷ As such, rifapentine for LTBI is not a good candidate for access as a serious or life-threatening medical emergency under the SAP.

History thus repeats itself with the UPHN, as the absence of alternative methods of access has meant a mechanism intended for other drugs to treat other conditions has been by necessity repurposed to access old Essential Medicines for Neglected Diseases, just as with the SAP before it. Despite being an afterthought rather than a driving force in the UPHN’s creation, rifapentine would very quickly prove to be the primary drug being accessed via this mechanism. This becomes obvious when looking at the UPHN List just over a year later, after the original one-year authorizations from the time of launch had expired. By July 2018, British Columbia had re-requested all three forms of diamorphine, but let requests for all six other drugs related to the opioid crisis lapse; in the interim, the Northwest Territories had requested one drug in response to the opioid crisis, and the Public Health Agency of Canada had requested two for use specifically in Correctional Service Canada facilities.¹²²⁸ By contrast, not only had First Nations and Inuit Health Branch renewed their request for rifapentine, nine other jurisdictions (Newfoundland, British Columbia, Nunavut, Manitoba, Yukon, Alberta, Northwest Territories, Ontario, and Public Health Agency of Canada for use in Correctional

¹²²⁷ Kiazky, S & T B Ball, “Latent tuberculosis infection: An overview” (2017) 43:3–4 Can Commun Dis Rep 62–66.

¹²²⁸ Health Canada, “List of Drugs for an Urgent Public Health Need”, version downloaded July 8, 2018

Service Canada Facilities) had requested the drug during the course of the year.¹²²⁹ This demonstrates widespread interest in access to rifapentine under the UPHN – notably more than for any of the individual opioid treatments the access mechanism was intended for. More recently, following multiple renewals of requests, and rather than continue the jurisdiction-by-jurisdiction requests for a drug being used across the country, PHAC has granted a blanket authorization for all jurisdictions in Canada to access rifapentine.¹²³⁰ This shows both the immediate need for off-patent Essential Medicines for Neglected Diseases, and the pent-up demand for mechanisms to effectively access them. As of 2022, access via the UPHN is highlighted in the most recent *Canadian Tuberculosis Standards* as the pathway for accessing a drug that still lacks Health Canada approval even as it has become part of the standard of care.¹²³¹

Despite the evident interest in access to rifapentine from across the country, it nevertheless does not appear to have been on Canada’s radar until late in the process of planning the public launch of the UPHN. As noted above, tuberculosis is not referenced in relation to the UPHN in the *Canada Gazette*; the first public reference to TB seems to be in the official press release announcing the launch of the UPHN, dated June 28, 2017.¹²³² That press release focuses on the opioid crisis; TB only receives a passing reference later on, in reference to the drugs found on the initial list.¹²³³ Unsurprisingly, the emphasis on opioids is also reflected in media coverage of the launch. For instance, the *Globe and Mail* story on the announcement bears the headline “Health Canada to allow imports of drugs needed to treat opioid

¹²²⁹ Health Canada, “List of Drugs for an Urgent Public Health Need”, version downloaded July 8, 2018

¹²³⁰ List of Drugs for an Urgent Public Health Need (20 April 2020). This was renewed 13 April 2021.

¹²³¹ Alvarez, Gonzalo G, Christopher Pease & Dick Menzies, “Chapter 6: Tuberculosis preventive treatment in adults” (2022) 6:sup1 *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine* 77–86, online: <<https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2039498>>.

¹²³² Health Canada. “Government of Canada enables new access to drugs in urgent public health situations”, (28 June 2017), online: <<https://www.canada.ca/en/health-canada/news/2017/06/government-of-canada-enables-new-access-to-drugs-in-urgent-public-health-situations.html>>.

¹²³³ Health Canada. “Government of Canada enables new access to drugs in urgent public health situations”, (28 June 2017), online: <<https://www.canada.ca/en/health-canada/news/2017/06/government-of-canada-enables-new-access-to-drugs-in-urgent-public-health-situations.html>>.

addiction”, and similarly only mentions tuberculosis once in passing, in language cribbed almost verbatim from Health Canada’s press release.¹²³⁴

The author reviewed a series of government documents regarding the creation of the UPHN, obtained via Access to Information (ATIP) request. This request proved to be a lengthy and frustrating ordeal; as of the submission of this thesis, some aspects of the author’s complaint to the Information & Privacy Commissioner of Canada regarding his request for these documents are still being investigated.¹²³⁵ Nevertheless, those documents that have been released, despite redactions, do strongly support the hypothesis that tuberculosis was an afterthought.¹²³⁶ For instance, drafts of the press release above indicate that TB was not even referenced in the initial version, but was added later.¹²³⁷ The remainder of the documents relating to the launch similarly underplay TB; internal emails refer to this event as a “media technical briefing on opioids”.¹²³⁸

This chain of events around the launch of the UPHN reflects the status of TB and rifapentine in the development of the UPHN more broadly. The first internal discussion of TB appears to have taken place well after the UPHN had been initially gazetted.¹²³⁹ The earliest released document referencing TB is an email on May 8, 2017, from Tom Wong (Chief Medical Officer of Public Health, Indigenous Services Canada), indicating he had chatted with Minister of Health Jane Philpott, and that Philpott was “very interested in the PHAC/FNIHB/HPFB exploration of improving rifapentine access” and as such was “keen in <sic> including rifapentine under the

¹²³⁴ Ubelacker, Sheryl. “Health Canada to allow imports of drugs needed to treat opioid addiction”, *Globe and Mail* (28 June 2017), online: <<https://www.theglobeandmail.com/news/politics/health-canada-to-allow-imports-of-drugs-needed-to-treat-opioid-addiction/article35487648/>>.

¹²³⁵ One element of the complaint has already been upheld, after the author demonstrated that the initial response from Health Canada stating no pertinent records around tuberculosis and the UPHN had been found among public submissions in response to the original *Gazette* publication had not been adequately conducted. He was able to do so rather convincingly, because his own pertinent submission addressing tuberculosis and the UPHN had not been identified and released.

¹²³⁶ All relevant files in authors possession.

¹²³⁷ Francis-Lamb, Laura, email: “RE: URGENT – revised Drugs for UPHN materials (due 1pm)” (22 June 2017).

¹²³⁸ Maddison, Anna, email: “Summary (with transcript): Media technical briefing on opioids – June 28” (28 June 2017).

¹²³⁹ “Regulations Amending the Food and Drug Regulations (Importation of Drugs for an Urgent Public Health Need)” *Canada Gazette*, Vol. 151, No. 16 — April 22, 2017.

importation of drugs in the setting of urgent public health needs”.¹²⁴⁰ This email was forwarded by Chief Public Health Officer of Canada Theresa Tam on May 11, 2017, as part of a message to Assistant Deputy Minister of Health Pierre Sabourin, in which she asks: “Would rifapentine be eligible to be put on the list for drugs needed for urgent public health event <sic>? It is a drug public health needs for dealing with tuberculosis outbreaks, which has rates similar to developing countries in Nunavut and very high rates in FN communities.”¹²⁴¹ The available evidence thus indicates it was not until some time after the UPHN had already been developed and published for public comment in April of 2017 that the Government of Canada recognized, even internally, that it could be used to access an Essential Medicine for tuberculosis.¹²⁴² Given the focus of this thesis, another point should be underscored: even as she queried whether an Essential Medicine for TB was eligible for a mechanism intended for an Urgent Public Health Need, Canada’s Chief Public Health Officer framed the issue as Nunavut having rates of TB “similar to developing countries”.¹²⁴³ This once more demonstrates both the scale of the problem and the perception that Neglected Diseases are an issue associated with LMICs, not with Canada.

The moral of the story is that not only are Neglected Diseases (and the drugs that treat them) neglected in Canada, they are also neglected in the process of regulatory reforms that might improve access to treatment. This is the case even when, as tuberculosis illustrates, they explicitly qualify as a “crisis” once someone pays attention. This thesis has already made reference to the Chief Public Health Officer of Canada’s 2018 report, *The Time Is Now: CPHO Spotlight on Eliminating Tuberculosis in Canada*. An example given within that report of tangible action being taken to tackle TB is that rifapentine “was recently placed on the List of Drugs for an Urgent Public Health Need in order to assist current TB elimination

¹²⁴⁰ FNIHB is the First Nations and Inuit Health Branch of Indigenous Services Canada and HPFB is the Health Products and Food Branch of Health Canada.

¹²⁴¹ Tam, Theresa, email: “Re: Rifapentine” (11 May 2017).

¹²⁴² The author notes that his own submission made to UPHN consultations – the same one not initially released in response to his ATIP request – was submitted on 7 May 2017, meaning it would have been the first released reference to tuberculosis.

¹²⁴³ Tam, Theresa, email: “Re: Rifapentine” (11 May 2017).

efforts”.¹²⁴⁴ The report neglects to mention that TB was only considered for the UPHN after the fact, with even the CPHO herself wondering about its eligibility; it also omits to clarify for the reader that the UPHN remains a stop-gap solution that does not actually bring this off-patent Essential Medicine for a Neglected Disease to market in Canada. The fact that this old Essential Medicine has been on the List of Drugs for an Urgent Public Health Need since it was first launched, and is now used across the country for what is explicitly labelled both a crisis and an urgent public health need, underscores the incongruity of the fact it remains unapproved in Canada. There is no indication that this state of affairs will change soon, however; at the time this thesis was written, no application for market approval had been submitted. The same is true for the European Medicines Agency, a potentially larger market, casting further doubt on Canadian approval in the near future.¹²⁴⁵ Meanwhile, even as access in Canada and Europe languished, a further indication for rifapentine – as part of a shorter regimen for treating active drug-sensitive TB – was added to the WHO MEML in 2021.¹²⁴⁶

The gap between access via the UPHN and formal market access is no mere technicality. Rifapentine’s absence from the formal market has practical consequences. For instance, in 2020, both the US FDA and Health Canada detected higher than acceptable levels of nitrosamines in samples of rifapentine and fellow WHO MEML-listed TB drug rifampin, creating a potential shortage of both drugs.¹²⁴⁷ Rifampin is formally available in both countries; rifapentine is only formally available in the United States. The FDA issued a public advisory for both

¹²⁴⁴ Tam, Theresa. *The Time Is Now: CPHO Spotlight on Eliminating Tuberculosis in Canada*, by Theresa Tam (Public Health Agency of Canada, 2018).

¹²⁴⁵ See e.g., KNCV Tuberculosis Foundation, “KNCV and European partners request Sanofi to take steps to register rifapentine with the EMA” (28 June 2016), online: <<https://www.kncvtbc.org/en/2016/06/28/kncv-and-european-partners-request-sanofi-to-take-steps-to-register-rifapentine-with-the-ema/>>.

¹²⁴⁶ For discussion of this regimen, see Dorman, Susan E et al., “Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis” (2021) 384:18 N Engl J Med 1705–1718, online: <<http://www.nejm.org/doi/10.1056/NEJMoa2033400>>.

¹²⁴⁷ This is one place where this thesis departs from the INN. The INN is rifampicin; however, both Canada and the United States generally refer to the drug as rifampin.

drugs.¹²⁴⁸ In Canada, as discussed earlier, drug companies are only required to report shortages for drugs with a DIN.¹²⁴⁹ Since an unmarketed drug does not have a DIN, there is no requirement to meet the same reporting obligations. Indeed, only the rifampin shortage has ever appeared on Canada's drug shortages reporting website. Health Canada itself only ever posted a public notice about the rifampin shortage.¹²⁵⁰ Given its public health importance, a notice regarding rifapentine was circulated to TB clinicians, but not publicly.¹²⁵¹ As international recognition increases of the value of rifapentine as part of shorter courses of treatment for drug-sensitive TB, in addition to its use for LTBI, Canadian patients risk being left behind once again in accessing the emerging standard of care.

Nevertheless, while it does not provide a direct pathway to market approval, the UPHN has contributed to increasing government recognition of the importance of removing disincentives for market entry, resulting in changes to Health Canada policy. The Health Canada guidance document on "Fees for the Review of Human and Disinfectant Drug Submissions and Applications" in effect early in the COVID-19 pandemic notes:

Fees may be waived for products on the List of Drugs for an Urgent Public Health Need as per the Access to Drugs in Exceptional Circumstances Regulations. If a submission or application is filed for a drug with the same medicinal ingredient, strength and route of administration, and is in a comparable dosage form to a drug on the list, it is eligible to be reviewed for free as long as no Drug Identification Number or Notice of Compliance has previously been issued for the product. However, if additional dosage forms, strengths

¹²⁴⁸ US Food & Drug Administration, "FDA recently became aware of nitrosamine impurities in certain samples of rifampin and rifapentine" (26 August 2020), online: <<https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamines-rifampin-and-rifapentine>>.

¹²⁴⁹ Reporting of shortages by the manufacturer is per Food and Drug Regulations - C.R.C., c. 870 (Section C.01.014.9).

¹²⁵⁰ Health Canada, "Update on the rifampin drug shortage" (15 March 2020), online: <<https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/72601a-eng.php>>.

¹²⁵¹ Personal correspondence, Richard Long (7 August 2020).

or routes of administration are included in the submission the full fee will be charged.¹²⁵²

In this way, Health Canada again shows some acknowledgement of the importance of market entry of key medicines as a component of the response to an Urgent Public Health Need. As yet, however, this incentive has not been sufficient to attract an application for rifapentine. Thus, the UPHN has provided a new tool for access to Essential Medicines for Neglected Diseases, but only as a by-product of measures tackling another very specific public health crisis. In February of 2022, Health Canada quietly granted formal approval to its first diamorphine product, produced by a Canadian company; rifapentine, by contrast, remains in limbo. In a final irony, the UPHN has never been utilized for any products used in the COVID-19 response, even as it has been used for flu vaccine during the same time period.¹²⁵³ This irony is compounded by the fact the jurisdiction-by-jurisdiction setup of the UPHN offers the closest thing Canada currently has to provincial-level approval of an unmarketed drug, per the twitter musings of Alberta Premier Jason Kenney discussed earlier. Nonetheless, Alberta has never attempted to use the UPHN for anything – other than for rifapentine for TB, which Alberta initiated before Kenney took office.¹²⁵⁴

The 2020 SAP reforms: Missed opportunities

Finally, in 2020, the regulations underpinning the SAP itself underwent the most serious overhaul in their fifty-plus year history. These reforms make some

¹²⁵² Health Canada, Guidance Document: Fees for the Review of Human and Disinfectant Drug Submissions and Applications, (Posted 4 November 2019, Effective 1 April 2020), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fees/fees-review-drug-submissions-applications-2019/document.html>>.

¹²⁵³ For instance, a November 2021 authorization for a request by PHAC for Fluzone High-Dose Quadrivalent influenza vaccine for use in adults 65 years of age and older in all jurisdictions is still in effect as of this writing.

¹²⁵⁴ Though even an Alberta-only importation would still have required the sign-off of both Alberta's Chief Medical Officer of Health and the Federal Minister of Health, making an importation driven purely by politics less probable. Houston, Adam, "Jason Kenney and the pharmaceutical pipeline", *Rabble* (5 May 2020), online: <<https://rabble.ca/blogs/bloggers/views-expressed/2020/05/jason-kenney-and-pharmaceutical-pipeline>>.

headway in addressing at least a few of the barriers flagged earlier in this thesis (and by this author elsewhere).¹²⁵⁵ In other areas, however, they fall short. And in still others, they are something of a double-edged sword; although the reforms as a whole improve access to some unapproved drugs in the short term, they may actually decrease the chances of old Essential Medicines receiving the formal authorization that would place them on equal footing with drugs currently on the market.

As with the UPHN, the Regulatory Impact Analysis Statement in the *Canada Gazette* accompanying the 2020 SAP reforms recognizes the fundamental failings of the market for certain drugs, including key themes highlighted in this thesis:

Evolving disease patterns and global health incidents with a domestic impact have emerged, requiring new drugs, which are often not available in Canada, as manufacturers may not submit these drugs to the Canadian market due to its small size. These conditions have reduced timely access to drugs for Canadian patients and animal owners.¹²⁵⁶

It also acknowledges the point, previously raised in this thesis, that the regulations underpinning the EDRP and the SAP were always meant as a bridging tool rather than a permanent mode of access:

¹²⁵⁵ See e.g., Houston, Adam R & Catherine-Marie Blais, “Neglected Tools: Access to Medicines for NTDs in Canada and the United States”, Health & Human Rights Journal (Blog) (1 September 2017), online: <<https://www.bhrjournal.org/2017/09/neglected-tools-access-to-medicines-for-ntds-in-canada-and-the-united-states/>>; Houston, Adam R et al., “Reforming Canada’s Special Access Programme (SAP) to improve access to off-patent essential medicines” (2018) 3:2 Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 100–107, online: <<http://jammi.utpjournals.press/doi/10.3138/jammi.2018.01.04>>; Houston, Adam R, “New Tricks for Old Drugs? Canada must change how it accesses Essential Medicines”, *Healthy Debate* (23 June 2020), online: <<https://healthydebate.ca/opinions/acceses-essential-medicines>>.

¹²⁵⁶ “Regulations Amending Certain Regulations Made Under the Food and Drugs Act (Sale of a New Drug for Emergency Treatment): SOR/2020-212”, Canada Gazette, Part II, (14 October 2020), Volume 154, Number 21, online: <<http://www.gazette.gc.ca/rp-pr/p2/2020/2020-10-14/html/sor-dors212-eng.html>>.

*Recognizing the length of time to bring a drug to market, set against the need to provide access to life-saving medication, the FDR was amended in 1966 to create emergency provisions that permit the sale of unauthorized drugs (drugs not approved in Canada) to provide Canadians with access to human and veterinary drugs in medical emergencies [emphasis added].*¹²⁵⁷

Nonetheless, the ultimate reforms fail to address multiple serious issues with the SAP, including some that have been raised for decades, and which were reiterated in further consultations in the lead-up to these reforms.¹²⁵⁸ One of these is the elephant in the room: that despite the acknowledgment in the RIAS that certain drugs are not coming to market in a timely manner, the reforms do not even hint at any corresponding measure to actually remedy that problem, even when the length of time to bring them to market stretches towards infinity. This issue had been raised once again in the consultations for these reforms, during which respondents “supported the idea of incentivizing manufacturers to bring long-standing SAP drugs through the more formal regulatory pathways with the use of foreign decisions, or waiving submission fees”.¹²⁵⁹ In fact, the specific issue of bringing to market (or in some cases back to market) old drugs that constitute the standard of care was explicitly highlighted in the consultation, along with some specific challenges around such drugs:

Respondents discussed the challenges of bringing to market old discontinued drugs that have become standard-of-care, for which the

¹²⁵⁷ “Regulations Amending Certain Regulations Made Under the Food and Drugs Act (Sale of a New Drug for Emergency Treatment): SOR/2020-212”, Canada Gazette, Part II, (14 October 2020), Volume 154, Number 21, online: <<http://www.gazette.gc.ca/rp-pr/p2/2020/2020-10-14/html/sor-dors212-eng.html>>.

¹²⁵⁸ Health Canada (Health Products and Food Branch), *Feedback from the consultation: renewal of Health Canada’s Special Access Programme (SAP)* (Health Products and Food Branch) (Undated). Obtained via request from Health Canada.

¹²⁵⁹ Health Canada (Health Products and Food Branch), *Feedback from the consultation: renewal of Health Canada’s Special Access Programme (SAP)* (Health Products and Food Branch) (Undated). Obtained via request from Health Canada.

chemistry and manufacturing information may not be available or up-to-date. Although often these drugs have become first line treatments, they may not meet the filing requirements for market authorization.¹²⁶⁰

This illustrates once again that the government has been made aware of the important issue of receiving, and maintaining, formal approval. As illustrated earlier in this thesis, the separation of the SAP and the formal approval process makes sense where there are concerns about using the SAP to bypass regulation for commercial gain, but at the same time ignores the realities of standard of care drugs that serve an important but unlucrative group of patients. Given the recognition of the unique circumstances of such drugs, it makes little sense to continue keeping formal access and access via the SAP in completely separate silos, at least in this limited context.

Even putting aside the failure to address the issue of market approval, the reforms also fall short in many areas that would improve access via the SAP in the continued absence of formal access.¹²⁶¹ For instance, participants in the consultation were asked “if they had concerns or experienced challenges with the current SAP” with an emphasis on “perceived gaps and process barriers”.¹²⁶² Given evidence presented thus far in this thesis, it is unsurprising that the responses “suggested that there was a need for better response times for SAP requests; more direct communication with requestors; increased openness about decisions with requestors; and, clearer expectations for practitioners with respect to reporting of patient outcomes and adverse drug reactions”.¹²⁶³ Even within the RIAS itself,

¹²⁶⁰ Health Canada (Health Products and Food Branch), *Feedback from the consultation: renewal of Health Canada's Special Access Programme (SAP)* (Health Products and Food Branch) (Undated). Obtained via request from Health Canada.

¹²⁶¹ Unintended consequences for market approval will be explored shortly.

¹²⁶² Health Canada (Health Products and Food Branch), *Feedback from the consultation: renewal of Health Canada's Special Access Programme (SAP)* (Health Products and Food Branch) (Undated). Obtained via request from Health Canada.

¹²⁶³ Health Canada (Health Products and Food Branch), *Feedback from the consultation: renewal of Health Canada's Special Access Programme (SAP)* (Health Products and Food Branch) (Undated). Obtained via request from Health Canada.

Health Canada acknowledges that concerns were raised about the transparency of the request approval process, but states that they are outside the reforms:

Other comments focused on operational improvements that could be made, such as more direct communication with requestors and increased openness about decisions with requestors. Health Canada has taken these comments under advisement as it considers operational improvements to the program; however, these improvements are outside of this regulatory proposal.¹²⁶⁴

While policy change may indeed be a nimbler means of addressing these issues, the SAP's record suggests it has not proven an effective one; the fact many of these issues have persisted for so long suggests that enshrining some standards within the regulations in areas such as timelines and transparent decision-making could help to promote accountability.¹²⁶⁵

Yet further key issues that remain unaddressed have particular implications for Neglected Diseases. For instance, the consultation acknowledges that “suggestions were put forward to improve the SAP, such as expanding the scope of products eligible under SAP for diseases with associated morbidity”, a suggestion which explicitly “includes tropical disease drugs to treat infectious diseases such as Strongyloidiasis and Echinococcosis, and chronic disease drugs”.¹²⁶⁶ Nevertheless, the SAP criteria were not ultimately expanded to ensure access to treatment outside of a medical emergency, leaving such patients without access until their conditions become sufficiently serious or life-threatening. Waiting to provide

¹²⁶⁴ “Regulations Amending Certain Regulations Made Under the Food and Drugs Act (Sale of a New Drug for Emergency Treatment): SOR/2020-212”, Canada Gazette, Part II, (14 October 2020), Volume 154, Number 21, online: <<http://www.gazette.gc.ca/rp-pr/p2/2020/2020-10-14/html/sor-dors212-eng.html>>.

¹²⁶⁵ As noted at other points in this thesis, although this thesis is not focused on the procedural fairness aspects of the SAP, it might be expected considerations such as a written decision with reasons would take on new importance in the post-Vavilov era. *Canada (Minister of Citizenship and Immigration) v. Vavilov*, 2019 SCC 65.

¹²⁶⁶ Health Canada (Health Products and Food Branch), *Feedback from the consultation: renewal of Health Canada's Special Access Programme (SAP)* (Health Products and Food Branch) (Undated). Obtained via request from Health Canada.

treatment until a patient is in serious condition or their life is threatened is self-evidently poor policy, both for the patient and for the health system. As discussed earlier, the regulatory foundation of the SAP for medical devices casts a far wider net, encompassing devices “for emergency use or if conventional therapies have failed, are unavailable or are unsuitable”.¹²⁶⁷ Without necessarily throwing the doors open quite so wide after “emergency use” when it comes to pharmaceuticals, the fact remains that Essential Medicines that are recognized as Essential Medicines already constitute “conventional therapies” by any logical measure. Whether by explicitly re-framing an emergency as lack of access to medicines established as the standard of care, or adding access to Essential Medicines as a separate category, the failure to expand the ambit of the SAP to clearly encompass such drugs was a missed opportunity.

The 2020 SAP reforms: Steps forward, steps back

Given this litany of issues *not* addressed, it is clear these overdue reforms leave much to be desired. Nevertheless, it must be recognized that some of the reforms are still likely to have positive impacts on patient access, at least for certain drugs and in the short term. To this end, the single biggest such regulatory change is that, under certain limited circumstances, the requesting practitioner will now no longer have to provide information in respect of the use, safety and efficacy of the drug. This information is no longer necessary where a) the drug has previously been authorized at least once under the SAP to address the same medical emergency; b) the drug is authorized for sale without terms and conditions for the same use by either the US FDA or the European Medicines Agency and c) the Minister of Health has not previously cancelled the drug’s DIN for safety reasons.¹²⁶⁸ Thus, the reforms go some distance towards acknowledging the realities of drugs that are regularly used and are marketed in other jurisdictions with Stringent Regulatory Authorities. While the precise manner of implementation of this new approach for previously requested drugs remained unclear at the time this thesis was

¹²⁶⁷ *Medical Devices Regulations* (SOR/98-282), s.69(2).

¹²⁶⁸ *Food and Drug Regulations* C.08.010 (2).

completed – a proposed online portal is still pending – the RIAS offers an estimate that this reduced information requirement could apply to between 30-40% of the requests to the SAP.¹²⁶⁹ Splitting the difference at 35%, it estimates this would apply to roughly 175 drugs and 5600 requests annually.¹²⁷⁰ The resulting savings in time and resources, by all parties to the application, recall suggestions made during the transition from EDRP to SAP in the mid-1990s, while still sensibly maintaining some level of gatekeeping for access to unapproved drugs in general.

Another change affecting access is that the patient's identity no longer needs to be known at the time of the request.¹²⁷¹ This provides flexibility for an amount of the drug to be ordered in advance. This is a potentially useful reform for mitigating delays when treatment is of the utmost urgency; as discussed earlier, the need to ensure timely access to just two Essential Medicines for a Neglected Disease, parenteral artesunate and parenteral quinine, had previously necessitated the creation of a whole new mechanism operating in conjunction with the SAP, the Canadian Malaria Network.¹²⁷² A complementary change is that the revisions also broaden the locations of permissible locations to which the drugs can be shipped, including community pharmacies; this should facilitate access to the drug for patients (even if questions of who will pay for drugs accessed in an increasing number of locations will ultimately implicate provinces, barring the intervention of a federal program like pharmacare).

These changes are likely to have a positive impact on faster access for individual patients. More ambiguously positive for patients in Canada are measures affecting drug makers. These too may have positive effects on access in the short

¹²⁶⁹ "Regulations Amending Certain Regulations Made Under the Food and Drugs Act (Sale of a New Drug for Emergency Treatment): SOR/2020-212", Canada Gazette, Part II, (14 October 2020), Volume 154, Number 21, online: <<http://www.gazette.gc.ca/rp-pr/p2/2020/2020-10-14/html/sor-dors212-eng.html>>.

¹²⁷⁰ "Regulations Amending Certain Regulations Made Under the Food and Drugs Act (Sale of a New Drug for Emergency Treatment): SOR/2020-212", Canada Gazette, Part II, (14 October 2020), Volume 154, Number 21, online: <<http://www.gazette.gc.ca/rp-pr/p2/2020/2020-10-14/html/sor-dors212-eng.html>>.

¹²⁷¹ *Food & Drug Regulations* C.08.010 (5).

¹²⁷² Public Health Agency of Canada, "Medical Access to Artesunate or Quinine for Malaria Treatment Streamlined in Canada through the Canadian Malaria Network (CMN)", online: <<https://www.canada.ca/en/public-health/services/travel-health/medical-access-artesunate-quinine-malaria-treatment.html>>.

term, but the potential long-term consequences raise some concerns. The biggest change in this regard is that the revised regulations permit the Minister to “issue a letter of authorization to the manufacturer of a new drug authorizing the holder of an establishment licence to import a specified quantity of the new drug” under certain conditions; this means they will be allowed to keep a stock of the drug in Canada, which can be sold in response to a request under the SAP.¹²⁷³ In other words, in contrast to mechanisms like the Canadian Malaria Network (where the drugs are held at a network of hospital sites), or provincial stockpiles of certain products obtained via the SAP like diphtheria antitoxin, the drug makers themselves are now allowed to pre-position a limited stock of their unapproved drugs for sale in Canada.

As with the aforementioned measures permitting ordering of a drug in the absence of a specific patient, prepositioning does offer the potential to hasten response times under the SAP, improving patient care. On the other hand, this measure also has the potential to act as a further disincentive for the manufacturer to take steps to formally bring the drug to market. After all, as the Supreme Court of Canada recognized, drug companies can already sell drugs via the SAP in unlimited quantities and in perpetuity.¹²⁷⁴ If it is made even simpler to sell a drug without going through the effort and expense of the regulatory process, why would a company do so? It must also be emphasized once more that this change has far wider repercussions than just old Essential Medicines for small numbers of patients. Many of the medicines accessed under the SAP are notably more lucrative than off-patent drugs for tuberculosis or parasitic infections. This includes pricey drugs for Rare Diseases, as well as novel treatments for conditions like cancer. As such, this new measure could actually serve to promote precisely what years of policy and case law have ostensibly been designed to prevent: permitting manufacturers to reap profits selling their new drugs in Canada while doing an end-run around regulation.

¹²⁷³ *Food and Drug Regulations* C.08.011.1 (1).

¹²⁷⁴ *Celgene Corp. v. Canada (Attorney General)*, 2011 SCC 1 (CanLII), [2011] 1 SCR 3 at para. 4.

Remarkably, the RIAS fails to even acknowledge this potential disincentive to seeking market authorization, let alone how it runs counter to years of policy. Given that previous policy and caselaw continuously underscored how the SAP is not equivalent to Health Canada approval, it is particularly surprising that this loosening of the reins on pharmaceutical companies comes with no evidence of a corresponding increase in oversight. This element of the reform has even drawn the attention of major law firms, who generally tend to pay little attention to the SAP; one blog post by a prominent firm remarks upon how it “is unclear at this stage if Health Canada will be increasing scrutiny of how these programs are used, given Health Canada’s recognition that some unapproved drugs are frequently requested and approved”.¹²⁷⁵ This further indicates that the ostensible focus on formal approval as the means of ensuring safety, efficacy and quality is in practice no longer quite so high a priority. For Essential Medicines already recognized as the standard of care, this new approach may be entirely appropriate; indeed, if a drug was unlikely to be formally marketed in any case, the result may be an improvement from the status quo. However, the benefits of extending this approach to all drugs obtained via the SAP, some of which may have little proven utility, are less clear-cut. At the very least, some clear cap or other restriction on the amount of profit earned off the importation of unapproved drugs would seem a logical consideration. This would be separate from other tools linked to pricing such as the PMPRB; given federal jurisdiction over access to unapproved drugs, and the fact access to such drugs is ostensibly an exception to federal regulation, measures of this kind should be feasible.¹²⁷⁶

¹²⁷⁵ McMahon, Eileen M, Teresa A Reguly & Albert Chan, “Health Canada streamlines program for access to unapproved drugs”, (16 November 2020), online: *Torys LLP* <<https://www.torys.com/insights/publications/2020/11/health-canada-streamlines-program-for-access-to-unapproved-drugs>>.

¹²⁷⁶ The issue of charging high prices for unapproved drugs has received attention for decades; however, the usual response has been to emphasize the jurisdiction of the PMPRB, which does not have authority over off-patent drugs. See e.g., Clark, Edie & Canadian Coordinating Office for Health Technology Assessment, *A Survey of investigational new drug and emergency drug release policies* (Ottawa, Ont.: Canadian Coordinating Office for Health Technology Assessment, 1991). Alternatives might include adopting a cost-plus model for unapproved drugs; this might be sufficiently unpopular with pharmaceutical companies as to be unfeasible, but is likely to be less contentious for older drugs whose production costs are already widely known.

Ultimately, however, unmarketed medicines will remain second-class drugs under the reformed SAP, even if there are some improvements to access. Continuing to treat Essential Medicines as second-class medications has numerous repercussions. This includes the previously discussed inability to access standard of care treatment for conditions falling short of the SAP “emergency” standard, despite the consequences for patients. Other shortcomings of the reforms are likely to have a particular impact on treatment of Neglected Diseases. As discussed earlier, availability only through the SAP has implications for off-label use, keeping unmarketed medicines at a disadvantage. This is further complicated by the fact that the simplified procedures of the 2020 SAP reforms apply only to approved indications for drugs that are being sourced from particular jurisdictions (the EU and the US). These jurisdictions may have narrower approved indications for some drugs; for instance, both albendazole and ivermectin have a greater number of indications on the WHO MEML than they do in either of those jurisdictions. As such, the simplified procedures of the revised SAP will *prima facie* not apply to the indications not approved in those jurisdictions, regardless of their WHO MEML status. Furthermore, some Essential Medicines for Neglected Diseases, like melarsoprol and diethylcarbamazine, are not marketed in either jurisdiction for any indication, meaning patients requiring these drugs will not reap the benefits of the reforms either.

Perpetuating the lack of formal market access will have still further negative repercussions. For instance, as noted earlier, those supplying unmarketed drugs do not have to fulfil other legal obligations required of marketed drugs. In fact, updated guidance documents for the SAP reiterate that a “drug obtained through the SAP is not subject to the same rules respecting good manufacturing practices, establishment licensing, labelling and adverse drug reaction reporting that apply to other new drugs”.¹²⁷⁷ The same applies to notification of drug shortages, which are

¹²⁷⁷ Health Canada, Special access program for drugs : guidance document for industry and practitioners (Revised 2022), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/special-access/drugs/guidance/sap-drugs-guid-ld-eng.pdf>>.

linked to a DIN.¹²⁷⁸ Not only do these differences in obligations have potential repercussions for patients and caregivers, the reforms may even exacerbate these issues. Avoiding all of these responsibilities could potentially be viewed as enough of an incentive by some companies that they could conceivably even tip the balance towards a marginally lucrative drug that might otherwise come to market, or stay on the market, being left to access via the SAP. If the option to pre-position stock of an unapproved drug to sell to as-yet unidentified patients had been available a few years earlier, would Merck still have chosen to bring ivermectin to the Canadian market, or would it have preferred to avoid the costs of gaining formal approval, and instead distribute their unmarketed drug at market rates? The fact the answer to this question is unclear is a sign that Health Canada would have benefitted from asking it.

Meanwhile, as discussed elsewhere in this thesis, absence from the formal market can also complicate other aspects of access such as insurance coverage (both public and private) for pharmaceuticals. In practice, formal market presence is not simply about safety, quality and efficacy, but about accessibility and affordability; it remains to be seen how provinces and private insurers will adapt. As a result, any improvements to timely patient access under the newly reformed SAP are a mixed blessing. As such, further reforms are necessary, at both the regulatory and policy levels. For instance, efforts to formalize the currently *ad hoc* efforts of Health Canada to encourage companies to bring drugs being accessed via the SAP to the formal market would be a welcome step. At the same time, putting aside the merits of the particular reforms to the SAP, the unprecedented scale of the reforms can be seen as a positive thing. It is also possible these measures may open the door for more effective reforms. For instance, the explicit use of specified foreign regulatory authorities to ease access to unmarketed drugs could be a stepping stone towards the use of foreign regulatory authorities to ease formal market entry, at least for Essential Medicines whose medical utility outweighs their commercial value.

¹²⁷⁸ Reporting of shortages by the manufacturer is per Food and Drug Regulations - C.R.C., c. 870 (Section C.01.014.9).

Chapter 12: The role of the state in the formal market

State intervention

Given the failure of the market to ensure formal access to off-patent Essential Medicines in HICs, the question becomes whether access can be addressed via the legal force of the state. In Canada, there is no legal mechanism to require a private company to bring a particular drug to market, or to permanently produce a drug against its will. The situation is similar in the United States. Indeed, in the US, where the idea has received more direct exploration in the courtroom, a “duty to manufacture” has been explicitly rejected on more than one occasion.¹²⁷⁹ For instance, in the 2013 case of *Schubert v. Genzyme Corp.*, involving a shortage of an enzyme replacement treatment for Fabry disease (a Rare Disease) due to manufacturing disruptions, the Federal District Court in Utah observed “Federal regulations require a manufacturer to report an interruption or discontinuance to the FDA, but there is no regulation imposing a duty to continue manufacturing”.¹²⁸⁰ In reaching its decision, the Court draws upon an earlier Florida case, this time involving product discontinuation. In that case, *Lacognata, et al. v. Hospira Inc.*, the plaintiff had made a similar claim after the sole manufacturer of an injectable form of Vitamin A exited the market; the claim was similarly unsuccessful.¹²⁸¹ The Court in *Schubert* found no difference between the manufacturer exiting the market in *Lacognata* and the manufacturing disruptions in the case before them.¹²⁸² The *Schubert* decision goes on to outline why no duty to manufacture has been imposed:

Imposing such a duty would prevent a manufacturer from ever ceasing production, require it to predict all potential demand, and further require it to maintain large stockpiles to prevent any shortages in case of production problems. Such an onerous rule is contrary to public

¹²⁷⁹ Janssen, William M. “A ‘Duty’ to Continue Selling Medicines” (2014) 40:4 Am J Law Med 330–392.

¹²⁸⁰ *Schubert v. Genzyme Corp.* (2013), No. 2:12-cv-00587-DAK, 2013 WL 4776286 at para.10-11.

¹²⁸¹ *Lacognata, et al. v. Hospira Inc.*, (2012) WL 6962884.

¹²⁸² *Schubert v. Genzyme Corp.* (2013), No. 2:12-cv-00587-DAK, 2013 WL 4776286 at para.9.

policy because it creates an enormous disincentive for potential providers of pharmaceuticals from entering the market in the first place and could stifle development of new therapies.¹²⁸³

These considerations are particularly relevant for medicines like those at the centre of this thesis, and highlight the challenges of effectively regulating medicines that the market has already failed. It is easy enough to suggest that pharmaceutical companies have an ethical obligation to ensure the continued availability of medicines, particularly Essential Medicines (a statement with which this author wholeheartedly agrees). Codifying that obligation is more difficult, however. For drugs with a legally sanctioned monopoly, such as those under patent, there is an argument that such rights should be accompanied by commensurate responsibilities. Indeed, the exclusive rights afforded a patentee can be used as leverage for production, utilizing the spectre of tools such as compulsory licensing to prod the patentee into action, or face losing their monopoly. However, this will only be effective if maintaining that monopoly is seen as valuable in the first place, and if there is an alternative producer waiting in the wings. In any case, such leverage is no longer available once a patent (or similarly sanctioned market exclusivity) expires. By this point, both sides of the societal “bargain” struck by the award of that monopoly have been met. As the Supreme Court of Canada has said, a patent “is a method by which inventive solutions to practical problems are coaxed into the public domain by the promise of a limited monopoly for a limited time”.¹²⁸⁴ Once the rights-holder has fully exercised its now-expired legal benefit, society has, ostensibly, gained unfettered access to the subject matter of the former monopoly. For a widely used drug with a large market, numerous potential producers may indeed be eagerly waiting to enter the market. For the drugs that are the particular

¹²⁸³ *Schubert v. Genzyme Corp.* (2013), No. 2:12-cv-00587-DAK, 2013 WL 4776286 at para.11.

¹²⁸⁴ *Apotex Inc. v. Wellcome Foundation Ltd.*, 2002 SCC 77, [2002] 4 S.C.R. 153 at para. 37. The SCC builds upon this same paragraph in *Apotex* to further explain the patent “bargain” in *Teva Canada Ltd. v. Pfizer Canada Inc.*, 2012 SCC 60, [2012] 3 S.C.R. 625 at para. 31. Fittingly, both cases involve pharmaceutical patents.

focus of thesis, however, this is not the case; there may simply be no commercial interest in grazing upon this corner of the knowledge commons.

This is not necessarily to say that the idea of imposing certain production obligations should necessarily be completely discounted within the broader context of the pharmaceutical trade, especially where a product is potentially highly lucrative. However, the benefits must be carefully weighed against the risks for drugs with little commercial appeal, and any intervention designed accordingly. For drugs like those addressed in this thesis, reticence to enter a market, let alone to subsequently maintain that market presence, is at the root of the problem in the first place. This raises a risk of imposing measures that could have the opposite effect from that intended. For instance, knowing it would be obliged to manufacture a drug in perpetuity – for instance as a condition of market authorization – would almost certainly be a major disincentive to market entry when it comes to commercially marginal products.¹²⁸⁵ Even the prospect of such legislation on the horizon could be an additional incentive for existing manufacturers to discontinue or divest from any products currently perceived as putting the company at future financial risk, thus potentially worsening the situation rather than improving it. It also seems unlikely bold proposals in this regard would be politically palatable; certainly, the proposal to use the revocation of a patent or NOC for one drug as leverage to gain access to another gained little traction when examined during the EDRP/SAP transition.¹²⁸⁶ In the case of an off-patent drug never sold in Canada in the first place, it is not even clear who such leverage could be applied to, given any company could in theory produce the drug.

As such, interventions have generally focused on carrots rather than sticks for encouraging market entry. One form of doing so has been to promote competition in pre-existing markets, a step that does not fill gaps where drugs are

¹²⁸⁵ There might be more elaborate ways to accomplish this in specific instances, for instance by placing strings on federal funding for new manufacturing facilities, requiring a certain number or percentage of “service drugs” to be manufactured, somewhat akin to new housing developments being required to provide a certain number of low-income units.

¹²⁸⁶ Sub-Committee on HIV/AIDS, *Compassionate Access to Investigational Therapies*, Second Report of the Standing Committee on Health. First Report of the Sub-Committee on HIV/AIDS Second Session, 35th Parliament (Parliament of Canada, 1996), Appendix III Problems associated with revoking either a patent or a notice of compliance.

absent, but does help to address concerns such as vulnerable or overpriced single-source drugs. For pharmaceuticals in general, increased competition is sound policy; having multiple sources of a drug should help to stabilize supply and lower prices.¹²⁸⁷ Here again, however, small market off-patent Essential Medicines pose interesting challenges for lawmakers. Where there is an existing market for a drug, encouraging additional sources may indeed help to decrease shortages and prevent exploitation such as off-patent trolling. Unfortunately, a small market seen as commercially unappealing for a *de facto* monopoly may look even less appealing for a competitor. Per a 2016 evaluation of the American drug landscape: “Of the 1,328 approved branded drugs, there is a sizable group, about 10 percent, whose exclusivities and patents have expired, but no drug companies have come forward to submit ANDAs”.¹²⁸⁸ This is a key dilemma in a market-driven pharmaceutical environment; tools premised on encouraging competition are ineffective when the market is such that an existing supplier may itself be on the cusp of discontinuance or divestment. As such, market entry may require further incentives beyond simply a smooth path to approval.

Nevertheless, in the United States, specific attempts were made to increase competition for sole-source drugs in the wake of the Special Commission Report into off-patent trolling.¹²⁸⁹ At the policy level, the US FDA initiated the Drug Competition Action Plan (DCAP). One component of the DCAP was the compilation of a list of “Off-Patent, Off-Exclusivity Drugs without an Approved Generic”.¹²⁹⁰ This list, updated twice a year, is a broad-reaching list of drugs with no listed patents or exclusivities and no approved generics. The list, in and of itself, provides a useful

¹²⁸⁷ It should be noted that a single competitor (i.e., a two-source market) may only have a small effect on drug prices; multiple sources are often needed to lower prices. See e.g., Dave, Chintan V, Abraham Hartzema & Aaron S Kesselheim, “Prices of Generic Drugs Associated with Numbers of Manufacturers” (2017) 377:26 N Engl J Med 2597–2598, online: <<http://www.nejm.org/doi/10.1056/NEJMc1711899>>.

¹²⁸⁸ Office of the Assistant Secretary for Planning and Evaluation, *Understanding Recent Trends in Generic Drug Prices*, ASPE Issue Brief (2016).

¹²⁸⁹ United States Senate Special Committee on Aging et al., *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System* (United States Senate, 2016).

¹²⁹⁰ As of this writing, the most recent version of the List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic was dated June 2022. Online: <<https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/list-patent-exclusivity-drugs-without-approved-generic>>.

reference point for identifying drugs potentially at risk of exploitation, or of exiting the market. This is complemented by the *FDA Reauthorization Act of 2017*, which introduced a number of reforms to address off-patent trolling through improved competition for such drugs.¹²⁹¹ In particular, the *Act* introduced a pathway for “Competitive Generic Therapies” to streamline approval, incentivized with a 180-day exclusivity for the first generic for drugs with only one manufacturer.¹²⁹² As the preceding discussion would suggest, however, these measures to encourage competing sources of these drugs were met with skepticism. As one commentator remarked: “There are reasons people don’t go after those products”.¹²⁹³

This is in stark contrast to more lucrative pharmaceuticals, where even a 180-day exclusivity can be a major incentive for a competitor to enter the US market in competition with the originator company. Such is the case with the broader generics exclusivities instigated under America’s well-known *Hatch-Waxman Act* (1984); among other provisions, the first generics company to file an ANDA asserting that a patent is invalid, or that no patent is infringed, is awarded 180 days of generic market exclusivity when their product comes to market.¹²⁹⁴ That companies would run the risk of costly litigation for a mere 180 days of generic exclusivity demonstrates once again that market incentives that are effective for blockbuster pharmaceuticals cannot simply be transposed to old drugs with a small, commercially unappealing market. They could even backfire; fears have been expressed that some of these FDA measures for sole-source drugs could make the problem of off-patent trolling worse by attracting unscrupulous attention to a list of the most vulnerable drugs.¹²⁹⁵

In any case, these new American measures targeting sole-source drugs have had mixed success bringing competitors to market. By April of 2022, 130 generics

¹²⁹¹ *FDA Reauthorization Act of 2017* (FDARA, P.L. 115-52), Sec. 508H.

¹²⁹² *FDA Reauthorization Act of 2017* (FDARA, P.L. 115-52), Sec. 508H.

¹²⁹³ Chakradhar, Shraddha & Roxanne Khamsi. “Angst about exclusivity: The potential cost of incentivizing makers of generic drugs” (2017) 23:10 Nat Med 1114–1116.

¹²⁹⁴ Section 505(j)(2)(A)(vii)(IV). See also Lietzan, Erika & Julia Post, “The Law of 180-Day Exclusivity” (2016) 71 Food and Drug Law Journal 327–400.

¹²⁹⁵ Chakradhar, Shraddha & Roxanne Khamsi. “Angst about exclusivity: The potential cost of incentivizing makers of generic drugs” (2017) 23:10 Nat Med 1114–1116.

had been approved in total as a result.¹²⁹⁶ This figure is itself slightly misleading; of these, just over half are actually deemed to meet eligibility criteria for exclusivity.¹²⁹⁷ This illustrates how some drugs attracted multiple competitors under the new legislation, with only one claiming the exclusivity prize. For instance, five sources of the Rare Disease drug penicillamine (previously trolled by Valeant) were approved, with the first receiving exclusivity.¹²⁹⁸ For Neglected Diseases, it has not been a roaring success, with only three Essential Medicines for Neglected Diseases making the approvals list.¹²⁹⁹ The most successful of these has been albendazole, attracting a notable eight new market-approved sources (though one has already been discontinued).¹³⁰⁰ The most recent, coming in December 2021, is liposomal amphotericin B, a leishmaniasis drug that will receive more attention later in this thesis. And the third is pyrimethamine, the drug that had first ignited interest in the problem of off-patent trolling.

For over five years, however, pyrimethamine remained an exorbitantly priced monopoly, well after Shkreli himself was behind bars, and even as the originator company, GSK, continued to market it elsewhere. Even with measures such as this enacted to promote competition, and, thanks to Shkreli, a going rate for Daraprim that would make a competing product sold at even a substantial discount a highly lucrative proposition, the first generic version of pyrimethamine was not approved by the US FDA until the end of February 2020, four and a half years after

¹²⁹⁶ US FDA, “Competitive Generic Therapy Approvals” online: <<https://www.fda.gov/drugs/generic-drugs/competitive-generic-therapy-approvals>>. Accessed 15 April 2022.

¹²⁹⁷ US FDA, “Competitive Generic Therapy Approvals” online: <<https://www.fda.gov/drugs/generic-drugs/competitive-generic-therapy-approvals>>. Accessed 15 April 2022.

¹²⁹⁸ US FDA, “Competitive Generic Therapy Approvals” online: <<https://www.fda.gov/drugs/generic-drugs/competitive-generic-therapy-approvals>>. Accessed 15 April 2022.

¹²⁹⁹ US FDA, “Competitive Generic Therapy Approvals” online: <<https://www.fda.gov/drugs/generic-drugs/competitive-generic-therapy-approvals>>. Accessed 15 April 2022.

¹³⁰⁰ US FDA, “Competitive Generic Therapy Approvals” online: <<https://www.fda.gov/drugs/generic-drugs/competitive-generic-therapy-approvals>>. Accessed 15 April 2022.

the widely-publicized price increase.¹³⁰¹ A few months after the first generic pyrimethamine was approved, Daraprim finally dropped off a prominent list of the 20 most expensive drugs in the United States, though its price remained considerably higher than it had been in early 2015.¹³⁰² As such, this attempt to entice new manufacturers to offer additional sources of an already marketed medicine has borne some fruit for certain drugs but cannot be considered a clear solution to overarching access concerns. It is also highly likely the previously trolled prices of drugs like albendazole and penicillamine served as a further incentive; after being *de facto* monopolies for so long, it seems unlikely either would have attracted so many market entrants at a pre-exploitation price with the mere incentive of a 180-day exclusivity against further competition. Given Canadian prices were not directly trolled to more commercially appealing heights, and drugs like pyrimethamine and albendazole are not formally marketed at all, similar measures to encourage competition are likely to be even less effective if transposed to the smaller Canadian market, at least for Essential Medicines for Neglected Diseases. It must also be remembered that these measures only apply to drugs that already had an approved source as a point of regulatory comparison to simplify the process; it does nothing to address the issue of Essential Medicines that have never been brought to market in the first place.

The cost of formal approval

So what else can be done to bring drugs formally to market, and subsequently keep them there? One of the suggestions that is often raised is that of waiving, or at least lowering, the costs of getting drugs approved, and in turn keeping them on the market. These fees can be substantial relative to the value of a commercially marginal drug; as of April 1, 2022, the fees for the examination of the submission of a new active substance – a category which, as discussed earlier, could include a

¹³⁰¹ US Food and Drug Administration, “FDA Approves First Generic of Daraprim”, (28 February 2020), online: <<https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-daraprim>>.

¹³⁰² Gelman, Max, “Martin Shkreli’s infamous Daraprim falls off top 20 most expensive drugs list”, *Endpoints News* (12 August 2020), online: <<https://endpts.com/martin-shkreli-infamous-daraprim-falls-off-top-20-most-expensive-drugs-list/>>.

decades-old Essential Medicine making its Canadian debut – is just short of half a million dollars.¹³⁰³ Furthermore, the costs do not end once the drug is marketed; for instance, there is an annual fee to sell a prescription drug.¹³⁰⁴ For a blockbuster drug, even the examination fee might seem like pocket change; for an old drug being sold to a handful of patients a year, even a few thousand dollars may serve as a disincentive to continue selling a drug, particularly if the same annual fee could be spent on a more profitable drug being made using those same facilities.

Here, it is worth highlighting that Canada has not always charged such fees; they were introduced in the mid-1990s as a cost-recovery measure.¹³⁰⁵ At the same time, the disincentive value of such fees should perhaps not be overstated either; many of the drugs for Neglected Diseases discussed in this thesis predate the imposition of such fees, demonstrating that the fees alone were not the deciding factor for bringing these drugs to market. Similarly, as discussed earlier, rifapentine has been eligible for a fee waiver for years as a drug found on the UPHN, yet no efforts have been made to bring it to market. Nevertheless, in a system dependent on commercial interest to drive the approval process, it is worth considering whether fees are at least part of the issue. Ironically, the recent trend in Canada has been towards higher fees, with a recent substantial increase.¹³⁰⁶ That said, a range of mitigation measures are currently possible according to current Health Canada guidance. These range from waivers and reductions for small businesses, to exemptions for drugs approved as EUNDS, for drugs found on the UPHN List (as with rifapentine) and, under certain circumstances, drugs for COVID-19.¹³⁰⁷ These

¹³⁰³ Health Canada, “Fees for Human Drugs” online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fees.html>>. Accessed Feb 10, 2022.

¹³⁰⁴ Health Canada, “Fees for Human Drugs” online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fees.html>>. Accessed Feb 10, 2022.

¹³⁰⁵ Lexchin, Joel, “Cost recovery by Health Canada and drug safety: a time-series analysis” (2018) 6:4 CMAJ Open E471–E477.

¹³⁰⁶ For instance, the examination fee increased from \$437,009 in 2021 to \$490,666 in 2022; the annual fee increased from \$2,749 to \$4,211 over the same period. Health Canada, “Fees for Human Drugs” online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fees.html>>. Accessed Feb 10, 2022.

¹³⁰⁷ Health Canada, “Guidance on evaluation fees for human drugs and disinfectants” (31 March 2021), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/funding-fees/fees-respect-human-drugs-medical-devices/right-sell-drugs-funding-fees-drugs-health-products.html>>.

point towards some degree of receptivity to waiving or lowering fees for important drugs as a means to encourage their market entry; however, existing measures do not cast the net widely enough to capture all the absent Essential Medicines highlighted in this thesis. A broader approach to fee waiver or mitigation for medically important drugs like Essential Medicines should be adopted, particularly where medical need outstrips commercial potential. Even though, as rifapentine demonstrates, a fee waiver cannot be relied upon to solve the problem, it nevertheless not only removes (or at least mitigates) one disincentive to market entry, but signals government support for the formal approval of drugs in this area. Although there are a range of possible strategies for identifying drugs worthy of such mitigation measures, tying a pathway for fee mitigation to Essential Medicines, including reference points such as the WHO MEML, a Canadian EML, and Canadian and international treatment guidelines, would provide a clear frame of reference while also limiting their scope.

To reiterate, removing or limiting fees is not a complete solution on its own, but one that should be considered in tandem with other reforms. At the same time, it is also important to consider how such measures might be exploited, and how that might be prevented. For instance, waivers or reductions in fees could be more effectively tied to projected and annual sales. Similarly, a company that benefits from measures to bring a useful but currently unavailable drug to the Canadian market should only reap the benefits of the waiver or reduction as long as its sales and its profits fall below those of a typical drug reaching the market in the typical way. Conversely, if it can be demonstrated that a useful drug is actually losing money once brought to market, consideration could be given to incentives to ensure its continued production. In turn, however, such measures merely complement other actions to nudge the market towards bringing drugs for Neglected Diseases to market in the first place.

Orphan Drugs & Neglected Diseases

Government measures to encourage the pharmaceutical industry to bring niche drugs to market are an area where “old” and “new” drugs blur together. This is also

an area where the impact on off-patent Essential Medicines for Neglected Diseases has been largely unintended by the drafters of those measures. This does not mean, however, that there are not valuable lessons to draw. The first part of this story has to do with Orphan Drugs. As noted earlier, Orphan Drug laws and policies are another area where Rare Diseases and Neglected Diseases intersect. While today the term “Orphan Drug” often carries implications of Rare Diseases, this has not always been the case. The history of the concept of Orphan Drugs has been engagingly recounted by others.¹³⁰⁸ However, as an exceedingly brief and oversimplified recap for the purposes of this thesis, Orphan Drugs are so named because they have no responsible guardians to shepherd them to market. They emerged in the wake of the more stringent pharmaceutical regulations that came into force in many countries, including Canada and the United States, in the aftermath of the thalidomide disaster.¹³⁰⁹ As noted earlier, these new requirements imposed new obligations on pharmaceutical companies; the consequence was that companies were less willing to go to the time and expense of meeting these new requirements for commercially marginal drugs. The reticence to bring such drugs to market left gaps in many countries that had made similar changes to their regulatory requirements. Importantly, the fact that many Orphan Drugs were already off-patent has long been recognized.¹³¹⁰ And as Villa and colleagues note when it comes to Orphan Drugs, there are today two categories of drug that draw particularly little attention from the pharmaceutical industry, “(i) drugs for rare diseases, and (ii) medicines for tropical diseases”.¹³¹¹

Attempts to address the issue of bringing Orphan Drugs to market are not new either. In 1983, landmark new legislation was introduced in the United States

¹³⁰⁸ To be clear, the actual story, including around the evolution of the orphan terminology itself, is more complex, but has little bearing on where orphan drugs fit into this thesis. See Mikami, Koichi, “Orphans in the Market: The History of Orphan Drug Policy” (2019) 32:3 Social History of Medicine 609–630, online: <<https://academic.oup.com/shm/article/32/3/609/4663001>>.

¹³⁰⁹ Cheung, Richard Y, Jillian C Cohen & Patricia Illingworth, “Orphan drug policies: implications for the United States, Canada, and developing countries” (2004) 12 Health Law J 183–200.

¹³¹⁰ Asbury, Carolyn H, “The Orphan Drug Act: The First 7 Years” (1991) 265:7 JAMA 893, online: <<http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.1991.03460070075046>>.

¹³¹¹ Villa, Stefano, Amelia Compagni & Michael R Reich. “Orphan drug legislation: lessons for neglected tropical diseases” (2009) 24:1 Int J Health Plann Mgmt 27–42, online: <<http://doi.wiley.com/10.1002/hpm.930>>.

in order to encourage R&D and commercialization of these Orphan Drugs.¹³¹² In a very American twist, successful passage of the legislation has been widely credited at least in part to awareness of the Orphan Drugs issue being intentionally raised on *Quincy, M.E.*, a popular medically-themed television show, as an advocacy tactic.¹³¹³ Although their television viewing habits are less overtly implicated, other countries would follow America's lead in introducing Orphan Drug legislation, including Japan in 1993, Australia in 1998, and in 2000 the EU.¹³¹⁴ Canada, however, still does not have equivalent legislation.¹³¹⁵ There is some irony to this; a key inspiration for the US legislation (and the seminal episode of *Quincy, M.E.*) is said to have been the experience of an American patient with Tourette's syndrome, who acquired the drug pimozide from Canada after being unable to do so in the United States.¹³¹⁶

As the same time, the influence of commercial motivations can also be seen in the early evolution of the legal definition of Orphan Drugs. As originally passed, America's *Orphan Drug Act (ODA)* contained no numerical reference point for the number of people in need of treatment. The *ODA* also initially applied only where "there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug", a definition that might seem rather

¹³¹² *Orphan Drug Act of 1983*. Pub L. No. 97-414, 96 Stat. 2049.

¹³¹³ Green, Joshua, "Jack Klugman's secret, lifesaving legacy", *Washington Post* (25 December 2012), online: <<https://www.washingtonpost.com/news/wonk/wp/2012/12/25/jack-klugmans-secret-lifesaving-legacy/>>. The initial episode in question is "Seldom Silent, Never Heard" (Episode 14 of Season 6); a follow-up episode on orphan drugs, "Give Me Your Weak" (Episode 3 of Season 8) aired shortly before the *ODA* was signed into law. The author wishes to note his exhaustive thesis research did in fact involve borrowing *Quincy, M.E.* DVDs from the public library.

¹³¹⁴ Villa, Stefano, Amelia Compagni & Michael R Reich. "Orphan drug legislation: lessons for neglected tropical diseases" (2009) 24:1 *Int J Health Plann Mgmt* 27-42, online: <<http://doi.wiley.com/10.1002/hpm.930>>.

¹³¹⁵ The closest it came was a discussion document outlining a possible framework in 2012. Health Canada, Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework, (13 December 2012), online: <<http://www.orpha.net/national/data/CA-EN/www/uploads/Initial-Draft-Discussion-Document-for-A-Canadian-Orphan-Drug-Regulatory-Framework.doc>>. For a discussion of the proposal, see Gibson, Shannon & Barbara von Tigerstrom, "Orphan drug incentives in the pharmacogenomic context: policy responses in the US and Canada" (2015) 2:2 *J Law Biosci* 263-291.

¹³¹⁶ Scheindlin, S, "Rare Diseases, Orphan Drugs, and Orphaned Patients" (2006) 6:4 *Molecular Interventions* 186-191, online: <<http://molinterv.aspetjournals.org/cgi/doi/10.1124/mi.6.4.2>>.

Neglected Disease-friendly; however, by the following year this had already been amended to create an alternative standard based on prevalence of 200,000 or fewer people in the USA, a subtle difference, but one opening the door to pricey Rare Disease drugs.¹³¹⁷ As Sarpatwari and Kesselheim note, if the prevalence threshold was ever an “adequate surrogate for profitability”, this is not longer the case today.¹³¹⁸ Along similar lines, an early criterion that the drug not be patentable was also quickly dropped.¹³¹⁹ The updated version is the version broadly reflected in the Orphan Drug legislation that followed in other jurisdictions.

In any case, America's *Orphan Drug Act* remains the best-known example of Orphan Drug legislation. It is also among the most generous; it contains both push incentives (such as tax breaks and other research supports, tied to an initial Orphan Drug designation of a drug that would be eligible for Orphan Drug status if it makes it to market) and pull incentives (such as a 7-year Orphan Drug exclusivity period for any drug actually receiving market approval as an Orphan Drug, which is independent of patent status and limits the circumstances under which the FDA will approve another drug containing the same active ingredient for the same indications during that period) to spur research and development for diseases considered rare in the United States.¹³²⁰ Some benefits thus accrue during the drug's development, while others only apply after its market approval. Overall, the *ODA* has been considered a success on many counts; from just a handful of approvals of Orphan Drugs in the years prior to the *ODA*, more than 500 drugs,

¹³¹⁷ Sarpatwari, Ameet & Aaron S Kesselheim. “Reforming the Orphan Drug Act for the 21st Century” (2019) 381:2 N Engl J Med 106–108, online: <<http://www.nejm.org/doi/10.1056/NEJMp1902943>>.

¹³¹⁸ Sarpatwari, Ameet & Aaron S Kesselheim. “Reforming the Orphan Drug Act for the 21st Century” (2019) 381:2 N Engl J Med 106–108, online: <<http://www.nejm.org/doi/10.1056/NEJMp1902943>>.

¹³¹⁹ Herder, Matthew, “When Everyone Is an Orphan: Against Adopting a U.S.-Styled Orphan Drug Policy in Canada” (2013) 20:4 Accountability in Research 227–269, online: <<https://www.tandfonline.com/doi/full/10.1080/08989621.2013.793120>>.

¹³²⁰ For a discussion, see Villa, Stefano, Amelia Compagni & Michael R Reich, “Orphan drug legislation: lessons for neglected tropical diseases” (2009) 24:1 Int J Health Plann Mgmt 27–42, online: <<http://doi.wiley.com/10.1002/hpm.930>>.

many with multiple indications, had been approved by 2020.¹³²¹ There is widespread agreement that at least some of these drugs would not have come to market otherwise.¹³²² It has been less successful, however, when it comes drugs for Neglected Diseases, despite finding themselves among the orphans. Although multiple Neglected Diseases have qualified as Rare Diseases for the purposes of initial Orphan Drug designation in the USA, including malaria, tuberculosis, leishmaniasis and both American and African trypanosomiasis, this initial Orphan Drug designation has been followed by just a handful of Neglected Disease drugs actually receiving FDA approval with Orphan Drug status.¹³²³

In assessing this handful of drugs, Trouiller and colleagues suggest there were only three genuinely innovative Orphan Drugs for Neglected Diseases approved between 1983 and 1997: eflornithine (the sleeping sickness drug discussed elsewhere) and two antimalarials, halofantrine and mefloquine.¹³²⁴ While a striking conclusion, their precise criteria for this determination of innovativeness are unclear.¹³²⁵ Nonetheless, the broader point regarding the paucity of Orphan Drugs for Neglected Diseases holds true; the list of other Essential Medicines approved as Orphan Drugs for Neglected Diseases during this period is a short one in any case. Undermining even this achievement, however, is the fact that many of this short list of medicines could already be found on the WHO MEML by the time they were approved as Orphan Drugs; this includes mefloquine, albendazole and amphotericin B. As such, while the *ODA* may have had some

¹³²¹ See e.g., National Organization for Rare Disorders (NORD) & Avalere, "Orphan Drugs in the United States" (2021), online: <https://rarediseases.org/wp-content/uploads/2021/03/NORD-Avalere-Report-2021_FNL-1.pdf>.

¹³²² Villa, Stefano, Amelia Compagni & Michael R Reich, "Orphan drug legislation: lessons for neglected tropical diseases" (2009) 24:1 Int J Health Plann Mgmt 27–42, online: <<http://doi.wiley.com/10.1002/hpm.930>>.

¹³²³ National Institutes of Health, List of Orphan FDA Orphan Drugs, online: <<https://rarediseases.info.nih.gov/diseases/fda-orphan-drugs/>>.

¹³²⁴ Trouiller, P et al., "Is orphan drug status beneficial to tropical disease control? Comparison of the American and future European orphan drug acts" (1999) 4:6 Tropical Medicine & International Health 412–420, online: <<https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-3156.1999.00420.x>>.

¹³²⁵ For instance, mefloquine was already on the WHO MEML well before it was approved as an orphan drug under the *ODA*, raising questions about how it was singled out by the authors as novel. Interestingly, while formerly approved in both countries, halofantrine is no longer marketed in the United States or in Canada, and has never been included on the WHO MEML.

influence on bringing Essential Medicines for Neglected Diseases to the US market, it also served to pioneer the practice of exploiting regulatory mechanisms by using one intended to foster innovation to simply obtain formal approval for pre-existing drugs. Indeed, pentamidine's Orphan Drug approval for *Pneumocystis carinii* and its subsequent high price after years of being accessed informally for sleeping sickness would prove to be an early example of a company exploiting an old drug it did not develop.¹³²⁶ Nor, crucially, has Orphan Drug status ensured that these Essential Medicines stay on the market; both clofazimine and eflornithine, for instance, were approved as Orphan Drugs but were subsequently discontinued in the United States.¹³²⁷

Concerns about the failure of Orphan Drug mechanisms to promote genuine innovation for Neglected Diseases have long been raised elsewhere in the world as well. For instance, in 1997, Olliario raised the question of whether then-proposed EU Orphan Drug regulation would accomplish anything for such diseases, concluding "whether or not an Orphan Drug policy exists, there seems to be little genuine research effort in the area of tropical diseases by the private sector".¹³²⁸ In the decades since, European legislation has, like its American counterpart, met with limited success when it comes to Neglected Diseases. By 2010, only 3.3% of Orphan Drug designations and a remarkable zero market approvals were for anti-infectious drugs of any kind.¹³²⁹ By 2020, there were indications that applications for Orphan Drug designation for infectious diseases, including Neglected Diseases like malaria,

¹³²⁶ Though previously available as an unmarketed drug for sleeping sickness via the CDC formulary, it was brought to market by LyphoMed Inc. for the treatment of *Pneumocystis carinii* pneumonia in HIV patients; despite neither inventing the drug nor conducting the studies that showed its utility against *Pneumocystis carinii*, LyphoMed promptly hiked the price. This reinforces the fact that reaping unearned rewards for old drugs is nothing new. Steinbrook, Robert, "Firm's Sharp Price Increase for AIDS Drug Attacked", *Los Angeles Times* (31 October 1987), online: <<https://www.latimes.com/archives/la-xpm-1987-10-31-mn-4490-story.html>>. See also "LyphoMed's pentamidine NDA on 'fast track' at FDA", *The Pink Sheet* (28 May 1984), online: <<https://pink.pharmaintelligence.informa.com/PS006646/LYPHOMEDs-PENTAMIDINE-NDA-ON-FAST-TRACK-AT-FDA>>.

¹³²⁷ Though as noted earlier in this thesis, eflornithine is available in Canada and the US in a topical form for facial hirsutism in women.

¹³²⁸ Olliario, P. "Will the fight against tropical diseases benefit from orphan drug status?" (1997) 2:2 *Trop Med Int Health* 113–115, online: <<http://doi.wiley.com/10.1046/j.1365-3156.1997.d01-234.x>>.

¹³²⁹ Wilson, Chris, "Orphan drugs and orphan drug legislation" in *Orphan Drugs* (Elsevier, 2013) 9.

leishmaniasis and MDR-TB had actually declined in Europe.¹³³⁰ The fact that the outcomes of Orphan Drug legislation have been disappointing for Neglected Diseases in American and Europe alike is particularly interesting given that the underlying motivations for such legislation differs between the two jurisdictions. As McCabe and colleagues point out, American legislation seems to justify this special regulatory status based on the cost of production and the value of innovation; by contrast, the EU seems to root its rationale in equity, stating patients with rare conditions should be entitled to the same quality of treatment as others.¹³³¹ Regardless of their philosophical underpinnings, neither the American nor European approach has enticed many pharmaceutical companies into the particular niche realm of innovation for Neglected Diseases.

In stark contrast to Neglected Diseases, Orphan Drugs for Rare Diseases of other kinds, such as rare genetic disorders, have proven remarkably popular with industry, and even more remarkably lucrative, particularly in the USA. By 2008, 43 drugs with an Orphan Drug designation, including 18 that had solely been approved in the United States as Orphan Drugs, had achieved blockbuster status, with over a billion dollars in annual global sales.¹³³² Furthermore, the number of Orphan Drug approvals for Rare Diseases continued to expand; a decade later, 58% of all drugs approved in the US were for a Rare Disease indication.¹³³³ Figures such as this have long raised concerns that programs to encourage Orphan Drugs for Rare Diseases have diverged from their original intent. The *ODA* has been criticized in relation to multiple efforts to exploit the system, like the practice of “salami slicing” by which companies seek out multiple narrow indications in order to

¹³³⁰ Mariz, Segundo, Kerstin Westermark & Bruno Sepodes, “Designation of orphan conditions in Europe: regulatory observations and considerations after implementation of regulation 141/2000” (2020) 8:6 Expert Opinion on Orphan Drugs 189–196, online: <<https://www.tandfonline.com/doi/full/10.1080/21678707.2020.1784720>>.

¹³³¹ McCabe, Christopher, Karl Claxton & Aki Tsuchiya. “Orphan drugs and the NHS: should we value rarity?” (2005) 331:7523 BMJ 1016–1019, online: <<http://www.bmj.com/lookup/doi/10.1136/bmj.331.7523.1016>>.

¹³³² Wellman-Labadie, Olivier & Youwen Zhou, “The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity?” (2010) 95:2–3 Health Policy 216–228, online: <<https://linkinghub.elsevier.com/retrieve/pii/S016885100900325X>>.

¹³³³ Sarpatwari, Ameet & Aaron S Kesselheim. “Reforming the Orphan Drug Act for the 21st Century” (2019) 381:2 N Engl J Med 106–108, online: <<http://www.nejm.org/doi/10.1056/NEJMp1902943>>.

qualify as Orphan Drugs, or – in a twist on the patterns of off-label usage discussed elsewhere in this thesis – the practice of seeking Orphan Drug approval while reaping money from sales for much wider off-label use for a more common condition.¹³³⁴ Some other jurisdictions have mitigating measures in place; for instance, in the EU, “the 10 years of exclusivity offered to rare disease drugs designated on the basis of a likelihood of generating insufficient return on investment can be reduced to 6 years if it can be shown that a drug is ‘sufficiently profitable’ after 5 years on the market”.¹³³⁵ Thus, there are certainly safeguards that can be built into Orphan Drug legislation more generally, though they fail to remedy the issue of Neglected Diseases.

Ultimately, the broader question of whether Canada should adopt its own Orphan Drug laws are beyond the scope of this thesis. The idea remains controversial; while some industry and patient groups have advocated for Canada to adopt an Orphan Drug strategy, other experts have been hesitant to adopt an American-style model.¹³³⁶ Regardless, given the experiences of other countries, a Canadian Orphan Drug program seems unlikely to have a major impact on the development of innovative new drugs for Neglected Diseases. After all, if large programs in the US and EU have been largely unsuccessful in promoting genuine innovation, it seems unlikely a Canadian program would succeed.¹³³⁷ Lack of success developing new drugs for a particular set of diseases is not a reason to actively exclude Orphan Drug programs from consideration, merely an indication to adjust expectations accordingly. Nevertheless, if Canada wants to initiate its own

¹³³⁴ Loughnot, David, “Potential interactions of the Orphan Drug Act and pharmacogenomics: a flood of orphan drugs and abuses?” (2005) 31:2–3 *Am J Law Med* 365–380; Daniel, Michael G et al., “The Orphan Drug Act: Restoring the Mission to Rare Diseases” (2016) 39:2 *American Journal of Clinical Oncology* 210–213, online: <<https://journals.lww.com/00000421-201604000-00017>>.

¹³³⁵ Sarpatwari, Ameet & Aaron S Kesselheim. “Reforming the Orphan Drug Act for the 21st Century” (2019) 381:2 *N Engl J Med* 106–108, online: <<http://www.nejm.org/doi/10.1056/NEJMp1902943>>.

¹³³⁶ See e.g., Herder, Matthew, “When Everyone Is an Orphan: Against Adopting a U.S.-Styled Orphan Drug Policy in Canada” (2013) 20:4 *Accountability in Research* 227–269, online: <<https://www.tandfonline.com/doi/full/10.1080/08989621.2013.793120>>.

¹³³⁷ At least on a large scale. This is not to discount the idea that individual drugs for Neglected Diseases can be, and indeed are, developed in Canada.

Orphan Drug policies, it needs to explicitly consider where Neglected Diseases fit into that policy.

As noted, the primary intent of Orphan Drug legislation has been to foster the development and market entry of novel drugs to serve small populations, not to encourage market entry of pre-existing drugs. While it may have had positive impacts in other areas, not only have the results for Neglected Diseases been underwhelming, the majority of drugs for Neglected Diseases approved under the *ODA* have been pre-existing treatments rather than genuinely novel ones. When the intent is to stimulate R&D for novel medicines, this outcome must be considered not merely a disappointment, but a prime example of the industry gaming the system. As a means of finally getting such medicines formal approval in HICs, however, they deserve closer inspection. Must attracting the market approval of old drugs be a completely unintended side-effect, or could it be an anticipated, and perhaps desired, outcome of such programs? Further lessons in this regard, including potential risks of such an approach, can be drawn from a subsequent American initiative, this time explicitly targeting Neglected Diseases.

Chapter 13: Targeting Neglected Diseases for market entry

The Priority Review Voucher and Chagas disease

While the American *ODA* encompasses Neglected Diseases within its broader scope, Neglected Diseases ultimately account for a very small proportion of drugs to receive Orphan Drug designation, let alone market approval. By contrast, a more recent mechanism was designed with the targeted goal of encouraging the development and commercialization of novel drugs specifically for Neglected Diseases. This mechanism is the Priority Review Voucher (PRV). The specific focus of the PRV has made the practice of introducing pre-existing Essential Medicines to the US market rather than promoting genuine innovation all the more obvious. As a result, the issue of promoting research into novel treatments for Neglected Diseases has become further tangled with the ostensibly separate issue of ensuring access to existing Essential Medicines. One of the key lessons of the PRV story is to underscore this difference between drugs that are genuinely innovative, and drugs that may be legally “new” to a particular jurisdiction despite being established as the standard of care both domestically and internationally. This issue has already been encountered in the Canadian context; Canada, however, has yet to take targeted action to bring such drugs to market, regardless of their novelty. There are thus lessons that Canada can learn before doing so. The potential pitfalls of conflating the two categories of novel and “new” drugs are exemplified by two decades-old Essential Medicines that have recently received US approval, at a time when the Neglected Disease they both treat has started to attract increased attention as a serious concern in HICs. The end result has been that two drugs that were not previously formally marketed in the US are now available. At the same time, for one of the drugs in particular, there was also a period of time where the PRV itself posed a serious threat to access. The story of these drugs ties together numerous threads woven throughout this thesis and illustrates, at multiple junctures, how actions taken in one country can have repercussions for access – positive and negative – elsewhere in the world.

The disease in question is another archetypal Neglected Disease: Chagas disease, also known as American trypanosomiasis (as distinct from African trypanosomiasis, aka sleeping sickness). Chagas disease is a protozoal disease caused by *Trypanosoma cruzi*. Native to South and Central America, its vector is insects of the *Triatominae* family, commonly known as kissing bugs. It is spread primarily through a complicated process which begins with the insect drinking blood from the lips of sleeping humans; the insect then defecates, and infected fecal matter enters the wound when the person rubs or scratches it.¹³³⁸ One important trait of the disease is that after the initial infection it enters a chronic phase, which can last for decades, and ultimately cause serious heart problems in around one third of patients.¹³³⁹ Such cardiac problems may ultimately necessitate major interventions like transplantation.¹³⁴⁰

Chagas has been estimated to affect between 6 and 8 million people worldwide.¹³⁴¹ The good news is that in the traditionally endemic regions of South and Central America new cases may be decreasing, primarily as a result of preventative measures targeting exposure to the insect vector.¹³⁴² At the same time, factors highlighted throughout this thesis also affect Chagas. For one,

¹³³⁸ Coura, José Rodrigues, “Chagas disease: what is known and what is needed--a background article” (2007) 102 Suppl 1 Mem Inst Oswaldo Cruz 113–122. Oral transmission via contaminated food can also occur. See e.g., Shikanai-Yasuda, Maria Aparecida & Noemia Barbosa Carvalho, “Oral transmission of Chagas disease” (2012) 54:6 Clin Infect Dis 845–852. Further methods of transmission, including from mother to child and via blood transfusion, will be discussed in more detail shortly.

¹³³⁹ Pérez-Molina, José A & Israel Molina, “Chagas disease” (2018) 391:10115 The Lancet 82–94, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673617316124>>; Marin-Neto, Jose Antonio et al., “Pathogenesis of Chronic Chagas Heart Disease” (2007) 115:9 Circulation 1109–1123, online: <<https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.624296>>.

¹³⁴⁰ See e.g., Kransdorf, E P et al., “Heart transplantation for Chagas cardiomyopathy in the United States” (2013) 13:12 Am J Transplant 3262–3268.

¹³⁴¹ Lidani, Kárita Cláudia Freitas et al., “Chagas Disease: From Discovery to a Worldwide Health Problem” (2019) 7 Front Public Health 166.

¹³⁴² Dias, JCP, AC Silveira & CJ Schofield, “The impact of Chagas disease control in Latin America: a review” (2002) 97:5 Mem Inst Oswaldo Cruz 603–612, online:

<http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0074-02762002000500002&lng=en&tlng=en>; Lidani, Kárita Cláudia Freitas et al., “Chagas Disease: From Discovery to a Worldwide Health Problem” (2019) 7 Front Public Health 166.

increased global migration has expanded its reach.¹³⁴³ For another, climate change could also do the same.¹³⁴⁴ Once overlooked outside of Latin America, it has become readily apparent that Chagas is a serious concern in many migrant communities living in countries not traditionally associated with the disease. This has led to calls for more attention in non-endemic countries.¹³⁴⁵ In 2010, the WHA approved a resolution recognizing the issue of Chagas both in endemic and non-endemic countries.¹³⁴⁶ Countries with high numbers of migrants from Chagas-endemic regions are, as might be expected, particularly vulnerable; given the long latency period, many migrants are not diagnosed until years after they were infected in their country of origin. The first case of Chagas wasn't described in Europe until the 1980s, seven decades after the disease had first been described elsewhere.¹³⁴⁷ By a decade ago, it was estimated that there were somewhere between 45,000 and 85,000 cases in Spain alone.¹³⁴⁸ A 2022 study comes in toward the lower end of this range, but estimates a prevalence of 2.1% in migrants from endemic countries.¹³⁴⁹ In the United States, it is estimated there are at least 300,000 cases, while some estimates are considerably higher.¹³⁵⁰ At the same time, such estimates are complicated by factors such as the disproportionate impact of

¹³⁴³ Pinazo, Maria-Jesus & Joaquim Gascon, "The importance of the multidisciplinary approach to deal with the new epidemiological scenario of Chagas disease (global health)" (2015) 151 *Acta Tropica* 16–20, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0001706X15300358>>.

¹³⁴⁴ Graves, Brittany N, *Climate Change and Chagas Disease in the Americas: A Qualitative Systematic Review* (MPH Dissertation, University of Texas, 2019) [unpublished].

¹³⁴⁵ Elkheir, Natalie et al., "Chagas disease in non-endemic settings" (2021) *BMJ* n901, online: <<https://www.bmj.com/lookup/doi/10.1136/bmj.n901>>.

¹³⁴⁶ World Health Assembly, "Chagas disease: control and elimination" (2010) WHA63.20, online: <https://www.who.int/neglected_diseases/mediacentre/WHA_63.20_Eng.pdf>.

¹³⁴⁷ Albajar-Vinas, P & J Jannin. "The hidden Chagas disease burden in Europe" (2011) 16:38 *Euro Surveill*.

¹³⁴⁸ Basile, L et al., "Chagas disease in European countries: the challenge of a surveillance system" (2011) 16:37 *Eurosurveillance*, online: <<https://www.eurosurveillance.org/content/10.2807/ese.16.37.19968-en>>.

¹³⁴⁹ Navarro, Miriam et al., "Estimating chagas disease prevalence and number of underdiagnosed, and undertreated individuals in Spain" (2022) 47 *Travel Medicine and Infectious Disease* 102284, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1477893922000308>>.

¹³⁵⁰ Montgomery, Susan P et al. "What Do We Know About Chagas Disease in the United States?" (2016) 95:6 *The American Journal of Tropical Medicine and Hygiene* 1225–1227, online: <<http://www.ajtmh.org/content/journals/10.4269/ajtmh.16-0213>>; Hotez, Peter J, "Neglected Infections of Poverty in the United States of America" (2008) 2:6 *PLoS Negl Trop Dis* e256, online: <<https://dx.plos.org/10.1371/journal.pntd.0000256>>.

Chagas on irregular migrants.¹³⁵¹ Emphasizing the growing profile of Chagas disease in HICs, the United States has also seen its own domestic vector-borne transmission.¹³⁵² Indeed, there is evidence that the implicated insects may not be new arrivals, but rather local species capable of spreading the disease.¹³⁵³ Over a decade ago, it was noted that although “not generally appreciated, *T. cruzi* is widely enzootic in the southern and southwestern regions of the United States, reaching northern California in the west and Maryland in the east”.¹³⁵⁴

The impacts of Chagas disease in HICs can be substantial; one study of the global economic burden of the disease suggests that the United States actually bears the highest financial burden for providing healthcare as a consequence of Chagas, with Spain high on the same list.¹³⁵⁵ While this is partly a function of the cost of healthcare in these countries relative to Latin America, rather than a usurpation of the overall burden of the disease itself, it nonetheless demonstrates the importance of the disease to public health in countries outside its traditional territory. While the United States and Spain are particularly affected, Chagas has been identified as a concern in countries from Australia to Japan.¹³⁵⁶ The list of affected countries includes Canada, where it has been diagnosed in migrant

¹³⁵¹ Such complications include irregular migrants facing additional barriers to healthcare, and the fact irregular migrants are disproportionately drawn from the same marginalized populations most at risk in their home countries. Bern, Caryn et al., “Chagas Disease in the United States: a Public Health Approach” (2019) 33:1 Clin Microbiol Rev, online: <<https://journals.asm.org/doi/10.1128/CMR.00023-19>>.

¹³⁵² Cantey, Paul T et al. “The United States Trypanosoma cruzi Infection Study: evidence for vector-borne transmission of the parasite that causes Chagas disease among United States blood donors: Vector-borne *T. cruzi* in US Donors” (2012) 52:9 Transfusion 1922–1930, online: <<http://doi.wiley.com/10.1111/j.1537-2995.2012.03581.x>>; Beatty, Norman L & Stephen A Klotz, “Autochthonous Chagas Disease in the United States: How Are People Getting Infected?” (2020) 103:3 The American Journal of Tropical Medicine and Hygiene 967–969, online: <<https://ajtmh.org/doi/10.4269/ajtmh.19-0733>>.

¹³⁵³ Curtis-Robles, Rachel et al., “Bionomics and Spatial Distribution of Triatomine Vectors of Trypanosoma cruzi in Texas and Other Southern States, USA” (2018) 98:1 Am J Trop Med Hyg 113–121; Garcia, Melissa N et al. “The 1899 United States Kissing Bug Epidemic” (2015) 9:12 PLoS Negl Trop Dis e0004117, online: <<https://dx.plos.org/10.1371/journal.pntd.0004117>>.

¹³⁵⁴ Kirchhoff, Louis V & Richard D Pearson. “The emergence of chagas disease in the United States and Canada” (2007) 9:5 Current Infectious Disease Reports 347–350.

¹³⁵⁵ Lee, Bruce Y et al., “Global economic burden of Chagas disease: a computational simulation model” (2013) 13:4 Lancet Infect Dis 342–348.

¹³⁵⁶ Schmunis, Gabriel A & Zaida E Yadon, “Chagas disease: a Latin American health problem becoming a world health problem” (2010) 115:1–2 Acta Trop 14–21.

populations since at least the 1970s.¹³⁵⁷ It was estimated that in 2006, at least 5500 migrants living in Canada were infected.¹³⁵⁸ As Chagas is not a reportable disease in Canada, a more recent estimate is hard to come by.¹³⁵⁹ However, it is not only migrants who are impacted. For instance, blood transfusion and organ donation pose a risk of transmission, while there have also been documented cases of congenital transmission in Canada.¹³⁶⁰

Increased recognition of the disease in HICs has encouraged steps to tackle it. Such measures include increased screening to capture undiagnosed cases of this disease that once slid under the radar.¹³⁶¹ They also include preventative measures such as policies to protect the blood supply and organ recipients from *T. cruzi* infection, as well as prevent congenital Chagas disease.¹³⁶² Canada, for instance, implemented measures along these lines some years ago. In 2007, Canadian Blood Services announced it would begin screening for Chagas disease as part of an overhaul of its processes.¹³⁶³ These changes followed at least two cases of transmission via blood transfusion in Canada.¹³⁶⁴ Demonstrating the complexity of the problem, a case of congenital transmission was identified a few years after these procedures were implemented, in the daughter of a woman whose only risk

¹³⁵⁷ Schipper, H et al., "Tropical diseases encountered in Canada: 1. Chagas' disease" (1980) 122:2 Can Med Assoc J 165–169, 171–172.

¹³⁵⁸ Schmunis, Gabriel A & Zaida E Yadon, "Chagas disease: a Latin American health problem becoming a world health problem" (2010) 115:1–2 Acta Trop 14–21.

¹³⁵⁹ Plourde, Pierre J, Kamran Kadkhoda & Momar Ndao, "Congenitally transmitted Chagas disease in Canada: a family cluster" (2017) 189:48 CMAJ E1489–E1492, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.170648>>.

¹³⁶⁰ Plourde, Pierre J, Kamran Kadkhoda & Momar Ndao, "Congenitally transmitted Chagas disease in Canada: a family cluster" (2017) 189:48 CMAJ E1489–E1492, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.170648>>.

¹³⁶¹ See e.g., Basile, L et al., "Chagas disease in European countries: the challenge of a surveillance system" (2011) 16:37 Euro Surveill.

¹³⁶² Schmunis, Gabriel A. "Epidemiology of Chagas disease in non endemic countries: the role of international migration" (2007) 102:suppl 1 Mem Inst Oswaldo Cruz 75–86, online: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0074-02762007000900013&lng=en&tling=en>; Bern, Caryn et al., "Chagas Disease in the United States: a Public Health Approach" (2019) 33:1 Clin Microbiol Rev, online: <<https://journals.asm.org/doi/10.1128/CMR.00023-19>>.

¹³⁶³ Comeau, P, "Canadian Blood Services to screen for Chagas disease" (2007) 177:3 Canadian Medical Association Journal 242–242, online: <<http://www.cmaj.ca/cgi/doi/10.1503/cmaj.070882>>.

¹³⁶⁴ Comeau, P, "Canadian Blood Services to screen for Chagas disease" (2007) 177:3 Canadian Medical Association Journal 242–242, online: <<http://www.cmaj.ca/cgi/doi/10.1503/cmaj.070882>>.

factor for Chagas disease was having received a blood transfusion in Manitoba prior to screening measures being in place.¹³⁶⁵ All of this illustrates how a Neglected Disease can impact policy once it becomes a little less neglected, and how taking concrete action to address a health risk is entirely possible even when only a small number of impacted people have been identified. However, access to treatment is obviously the focus of this thesis, and it is here that many countries have been slower to take decisive action.

The achievements of the Brazilian physician Dr. Carlos Chagas regarding the disease that bears his name are both remarkable and unique; he not only discovered a new disease, but also its underlying pathogen and its vector.¹³⁶⁶ Breaking slightly with a recurring theme of this thesis, Dr. Chagas did not win a Nobel Prize, though he was nominated in both 1913 and 1921 (the latter loss must have been particularly disappointing, as the Nobel Prize in Physiology or Medicine was not awarded to anyone at all that year).¹³⁶⁷ By contrast with the spirited efforts of Dr. Chagas, subsequent breakthrough discoveries have been in shorter supply. Currently, there are only two drugs approved for Chagas disease anywhere in the world (although fexinidazole, the novel sleeping sickness drug mentioned elsewhere in this thesis, is currently thought to hold promise).¹³⁶⁸ These two drugs are benznidazole and nifurtimox. Both have been in use for over half a century, and both have been Essential Medicines on the WHO MEML for decades.¹³⁶⁹ Nonetheless, until very recently, they were generally not formally available outside

¹³⁶⁵ Fearon, Margaret A et al. "A case of vertical transmission of Chagas disease contracted via blood transfusion in Canada" (2013) 24:1 Can J Infect Dis Med Microbiol 32–34.

¹³⁶⁶ Lidani, Kárita Cláudia Freitas et al., "Chagas Disease: From Discovery to a Worldwide Health Problem" (2019) 7 Front Public Health 166.

¹³⁶⁷ Kropf, Simone Petraglia & Magali Romero Sá, "The discovery of *Trypanosoma cruzi* and Chagas disease (1908-1909): tropical medicine in Brazil" (2009) 16 Suppl 1 Hist Cienc Saude Manguinhos 13–34; Coutinho, Marília, Olival Freire Jr & João Carlos Pinto Dias, "The noble enigma: Chagas' nominations for the Nobel Prize" (1999) 94:suppl 1 Mem Inst Oswaldo Cruz 123–129, online: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0074-02761999000700012&lng=en&tlng=en>.

¹³⁶⁸ Deeks, Emma D, "Fexinidazole: First Global Approval" (2019) 79:2 Drugs 215–220.

¹³⁶⁹ Since 1987 and 1977, respectively; nifurtimox has also been indicated for sleeping sickness since 2009.

of a few – and certainly not all – endemic countries in Latin America.¹³⁷⁰ During the period that this thesis was being crafted, however, both drugs received approval from the US FDA, long after each was first included on the WHO MEML. Both followed a similar pathway to get there, though one's journey attracted considerably more attention.

Dodging a bullet: Benznidazole

The higher profile story, by a considerable margin, has been that of benznidazole. Benznidazole has been in use in some Latin American countries since 1971, when it was brought to market by Roche (using the tradenames Rochagan and Radanil). However, in a pattern that should be unsurprising by this point, its market status in the 21st Century has been complex. In 2003, Roche divested themselves of benznidazole entirely.¹³⁷¹ Despite doing so nearly two decades ago, Roche somewhat shamelessly still lists benznidazole on its Essential Medicines webpage.¹³⁷² In an intriguing arrangement, Roche transferred the rights not to another pharma company but to the government of the Brazilian state of Pernambuco, with the drug to be produced by the state's public laboratory, the Laboratório Farmaceutico do Estado de Pernambuco (LAFEPE).¹³⁷³ As with Eli Lilly's divestment of cycloserine, this may reflect some recognition that an Essential Medicine should not be thought of purely as a private commercial commodity; at the same time, it may also reflect a lack of other willing takers. In another parallel to Lilly's divestment to the Chao Center, however, poor planning – this time

¹³⁷⁰ While the author has encountered passing references to nifurtimox being available in Germany – as discussed later, it is made by the German company Bayer – this no longer seems to be the case, if in fact it ever was. See e.g., Guggenbühl Noller, Jessica Michelle et al., "Describing nearly two decades of Chagas disease in Germany and the lessons learned: a retrospective study on screening, detection, diagnosis, and treatment of *Trypanosoma cruzi* infection from 2000 – 2018" (2020) 20:1 BMC Infect Dis 919, online: <<https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05600-8>>.

¹³⁷¹ Médecins Sans Frontières, *The Shortage of Benznidazole Leaves Thousands of Chagas Patients without Treatment*, Briefing Document, (Médecins Sans Frontières, 2011), online: <<https://doctorswithoutborders.org/sites/default/files/2018-08/Chagas%20briefing%20paper%20Final.pdf>>.

¹³⁷² Roche, "Developing essential medicines", online: [roche.com](https://www.roche.com/sustainability/access-to-healthcare/ath_who.htm) <https://www.roche.com/sustainability/access-to-healthcare/ath_who.htm>.

¹³⁷³ Molina, I et al., "Toxic Profile of Benznidazole in Patients with Chronic Chagas Disease: Risk Factors and Comparison of the Product from Two Different Manufacturers" (2015) 59:10 Antimicrob Agents Chemother 6125–6131.

including on the part of the government – ultimately undermined the outcome. After the LAFEPE product was registered with the Brazilian Drug Regulatory Authority (Agência Nacional de Vigilância Sanitária - ANVISA), Roche withdrew their own registration, leaving LAFEPE as the only global producer.¹³⁷⁴ However, other issues were encountered in Brazil, including regulatory delays in production of the sole source of API switching from Roche to the Brazilian company Nortec Química; this led to shortages once the last remaining Roche supplies of both API and finished product began to expire.¹³⁷⁵ Organizations such as MSF publicly castigated this lack of coordination by the Brazilian government for creating these delays.¹³⁷⁶

While the shortage created obvious concerns for Brazil and its Chagas-endemic neighbours, it also threatened patients elsewhere in the world. Canada, where benznidazole was (and remains) accessible only through the Special Access Programme, was among the countries that felt the impact of the global shortage.¹³⁷⁷ In Spain, concerned physicians described the situation as one where the “current shortage of benznidazole makes Chagas disease a neglected tropical disease also in developed countries”.¹³⁷⁸ Their counterparts in Italy similarly declared:

The shortage of benznidazole is one of the examples of both the globalization of health needs for a single NTD, a condition thought to be confined to the south of the world, and of the reasonings of the

¹³⁷⁴ Médecins Sans Frontières, *The Shortage of Benznidazole Leaves Thousands of Chagas Patients without Treatment*, Briefing Document, (Médecins Sans Frontières, 2011), online: <<https://doctorswithoutborders.org/sites/default/files/2018-08/Chagas%20briefing%20paper%20Final.pdf>>.

¹³⁷⁵ Médecins Sans Frontières, *The Shortage of Benznidazole Leaves Thousands of Chagas Patients without Treatment*, Briefing Document, (Médecins Sans Frontières, 2011), online: <<https://doctorswithoutborders.org/sites/default/files/2018-08/Chagas%20briefing%20paper%20Final.pdf>>.

¹³⁷⁶ Médecins Sans Frontières, *The Shortage of Benznidazole Leaves Thousands of Chagas Patients without Treatment*, Briefing Document, (Médecins Sans Frontières, 2011), online: <<https://doctorswithoutborders.org/sites/default/files/2018-08/Chagas%20briefing%20paper%20Final.pdf>>.

¹³⁷⁷ Fearon, Margaret A et al. “A case of vertical transmission of Chagas disease contracted via blood transfusion in Canada” (2013) 24:1 Can J Infect Dis Med Microbiol 32–34.

¹³⁷⁸ Navarro, Miriam et al., “Benznidazole shortage makes chagas disease a neglected tropical disease in developed countries: data from Spain” (2012) 87:3 Am J Trop Med Hyg 489–490.

worldwide pharmaceutical market. Such an illogical situation, in which lifesaving treatment for millions of people depends wholly on a single pharmaceutical company that, in this case, is also subject to logistical issues, local political decisions, and lack of support from the Ministry of Health, should make everyone think. In this absurd context, the health of all Chagas patients in the world is pending on the Brazilian Ministry of Health's will... while the WHO gives essential indications, NGOs accuse the system of neglecting millions of people with CD, and each country with Chagas patients does all it can to secure doses of the drug and define distribution criteria.¹³⁷⁹

This effectively captures the situation where a drug needed around the world is vulnerable to the caprices of the market and the tribulations of a sole source. In 2012, a second source of benznidazole finally entered the global market, produced by the Argentinian company ELEA (Laboratório Endocrínico Argentino) as a public-private partnership.¹³⁸⁰ Furthermore, ELEA production drew upon a new source of API from the affiliated Argentinian company Maprimed.¹³⁸¹ Although ELEA guaranteed production and distribution throughout Latin America, it came with a higher price tag that affected access for some patients.¹³⁸² Internationally, the LAFEPE product was also sold at a high price by its distributor.¹³⁸³

¹³⁷⁹ Bonati, Maurizio & Valeria M Confalonieri. "Global rights for global diseases. The shortage of benznidazole case" (2012) 22:eLetters Supplement European Journal of Public Health, online: <https://academic.oup.com/eurpub/article/doi/10.1093/eurpub/el_316/2547684>.

¹³⁸⁰ Dias, João Carlos Pinto, Jose Rodrigues Coura & Maria Aparecida Shikanai Yasuda, "The present situation, challenges, and perspectives regarding the production and utilization of effective drugs against human Chagas disease" (2014) 47:1 Rev Soc Bras Med Trop 123–125, online: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0037-86822014000100123&lng=en&tng=en>.

¹³⁸¹ Dias, João Carlos Pinto, Jose Rodrigues Coura & Maria Aparecida Shikanai Yasuda, "The present situation, challenges, and perspectives regarding the production and utilization of effective drugs against human Chagas disease" (2014) 47:1 Rev Soc Bras Med Trop 123–125, online: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0037-86822014000100123&lng=en&tng=en>.

¹³⁸² Alpern, Jonathan D, Rogelio Lopez-Velez & William M Stauffer. "Access to benznidazole for Chagas disease in the United States—Cautious optimism?" (2017) 11:9 PLoS Negl Trop Dis e0005794, online: <<https://dx.plos.org/10.1371/journal.pntd.0005794>>.

¹³⁸³ Dias, João Carlos Pinto, Jose Rodrigues Coura & Maria Aparecida Shikanai Yasuda, "The present situation, challenges, and perspectives regarding the production and utilization of effective drugs

The story thus far demonstrates a range of pitfalls, including the importance of API as well as the finished product, the fact that state involvement in production is by no means a guaranteed panacea, and the global repercussions of a pause in production by the sole source of an Essential Medicine. Furthermore, by this juncture in the story, even with two producers, benznidazole had never been formally marketed in most HICs, including Spain, Canada and the United States, despite a need for access. For one of these countries, this would soon change. The need for stable, affordable and accessible global access was almost certainly not, however, the primary motivation behind the first mover in the high-profile attempt to get FDA approval. Rather, that incentive came in August 2015, when the US FDA issued an order adding Chagas to the list of tropical diseases eligible for a Priority Review Voucher.¹³⁸⁴

Priority Review Voucher (PRV)

As introduced above, the Priority Review Voucher (PRV) is an American initiative, enshrined in law, that was specifically designed to tackle the dearth of new drugs for Neglected Diseases. The idea of the PRV was proposed by Ridley and colleagues in a 2006 paper.¹³⁸⁵ The concept was taken up by lawmakers remarkably quickly; the following year, the US *Federal Food, Drug & Cosmetic Act* was amended to create such a system.¹³⁸⁶ The idea also received support from the likes of software guru turned global health philanthrocapitalist Bill Gates.¹³⁸⁷ Although the *Orphan Drug Act* had encompassed Neglected Diseases two decades earlier, the PRV was the first major regulatory incentive specific to Neglected Diseases themselves.

against human Chagas disease" (2014) 47:1 Rev Soc Bras Med Trop 123–125, online: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0037-86822014000100123&lng=en&tlng=en>.

¹³⁸⁴ US Food and Drug Administration, "Designating Additions to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act" 80 FR 50559 (20 August 2015), online: <<https://www.federalregister.gov/documents/2015/08/20/2015-20554/designating-additions-to-the-current-list-of-tropical-diseases-in-the-federal-food-drug-and-cosmetic>>.

¹³⁸⁵ Ridley, David B, Henry G Grabowski & Jeffrey L Moe, "Developing drugs for developing countries" (2006) 25:2 Health Aff (Millwood) 313–324.

¹³⁸⁶ *Food and Drug Administration Amendments Act of 2007*, Pub. L. No. 110-85, § 1102, 121 Stat. 823, 972 (2007).

¹³⁸⁷ This thesis will tactfully avoid wading into the question of the overall role of Bill Gates in global health. Doshi, P, "US incentive scheme for neglected diseases: a good idea gone wrong?" (2014) 349:Jul21 1 BMJ g4665–g4665, online: <<https://www.bmj.com/lookup/doi/10.1136/bmj.g4665>>.

It should be noted that here once again, the terminology around Neglected Diseases becomes fuzzy. While the US FDA refers to the resulting initiative as the Tropical Disease PRV Program, Ridley and colleagues refer to Neglected Diseases in their original proposal, and several diseases eligible for the program since the beginning, notably tuberculosis, are decidedly not specific to the tropics. The formal definition for eligible diseases similarly has no latitudinal restrictions. To be added to the list of PRV-eligible Tropical Diseases, a condition must be an “infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations”.¹³⁸⁸ As such, the PRV targets new treatments for precisely the diseases under discussion in this thesis. The list of eligible diseases has also increased over time; indeed, as discussed below, Chagas itself was not added until some years after the PRV had been in place. In deciding whether to add diseases, the US FDA looks to a range of sources; one explicit consideration is whether a disease is classified as an NTD by the WHO.¹³⁸⁹ Similarly, in determining whether there is no significant market in developed nations, it uses a numerical benchmark for prevalence:

If the prevalence of a disease in developed countries is less than 0.1 percent of the population of those countries, it is unlikely that ordinary market forces will offer a sufficient incentive to drive the development of new preventions or treatments. Thus, it is unlikely that there will be a “significant market” for the disease's treatment in those countries.¹³⁹⁰

¹³⁸⁸ *Food, Drug & Cosmetic Act* 21 U.S.C. ch. 9 § 301 s. 524(a)(3)(R).

¹³⁸⁹ US FDA, “Designating Additions to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act” 80 FR 50559 (20 August 2015), online: <<https://www.federalregister.gov/documents/2015/08/20/2015-20554/designating-additions-to-the-current-list-of-tropical-diseases-in-the-federal-food-drug-and-cosmetic>>.

¹³⁹⁰ US FDA, “Designating Additions to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act” 80 FR 50559 (20 August 2015), online: <<https://www.federalregister.gov/documents/2015/08/20/2015-20554/designating-additions-to-the-current-list-of-tropical-diseases-in-the-federal-food-drug-and-cosmetic>>.

The PRV itself has sometimes been informally described as a VIP pass to the front of the approval line.¹³⁹¹ This is not quite accurate. Possession of a PRV does, however, permit the holder of the voucher to receive a 6-month “priority” review from the US FDA, rather than the standard 9-month review, for another drug that would not otherwise qualify for priority review. This means a company with a PRV received for developing a novel Neglected Disease drug can use that voucher to get their next anticipated blockbuster drug out of the gate faster. The PRV thus cleverly addresses one of the key stumbling blocks to using market incentives to encourage the development of new drugs perceived as having limited market value, such as those for Neglected Diseases: it applies the incentive to a different and more commercially appealing drug.

Another important element of its design is that the PRV itself is also transferable; a company who has earned a PRV but does not have something it wants to hurry through the queue can sell it to another company that does. As such, a PRV can itself be a valuable asset; transfer prices have ranged from \$67 million USD to \$350 million.¹³⁹² At the same time, using a PRV does come with its own fee; while the precise amount differs every year, it has consistently been in the low seven figures.¹³⁹³ It is a reflection of the vast differences in market appeal for different drugs that companies are willing to pay tens or even hundreds of millions to acquire, plus another million to use, a PRV that itself exists as an incentive to develop drugs that these same companies otherwise show little interest in researching. It is also worth noting that using a PRV is no guarantee that a drug that undergoes priority review will be approved; simply the *possibility* of an accelerated

¹³⁹¹ See e.g., Tribble, Sarah Jane, “A Golden Ticket That Fast-Tracks A Drug Through The FDA”, *KHN News* (29 September 2016), online: <<https://khn.org/news/a-golden-ticket-that-fast-tracks-a-drug-through-the-fda/>>.

¹³⁹² United States Government Accountability Office, *Drug Development - FDA's Priority Review Voucher Programs*, Report to Congressional Committees GAO-20-251 (2020).

¹³⁹³ It is based on the difference between the average cost incurred by the US FDA to review a human drug application designated as priority review and one not subject to priority review in the previous fiscal year. At \$1,360,879, the fee for the 2021 fiscal year is below average. Food and Drug Administration, Health and Human Services (HHS), “Fee Rate for Using a Tropical Disease Priority Review Voucher in Fiscal Year 2021” (7 October 2020) 4164-01-P, online: <<https://public-inspection.federalregister.gov/2020-22191.pdf>>.

approval is deemed worth tens or even hundreds of millions of dollars.¹³⁹⁴ The prospect of a few extra months of sales of the next Lipitor or Viagra has thus proven an enticement to earn a PRV, or at least to pay large amounts for the PRVs earned by others. And while the eponymous transferable voucher is the primary incentive of the PRV, it is not the only one. For instance, the “tropical disease” drug that earns the PRV in the first place is itself granted a five-year period of exclusivity after approval, regardless of patent status. Thus, even though the Tropical Disease drug is one that, by legal definition, is one that is unlikely to have a significant market in the US, it nonetheless also benefits from market exclusivity.

The underlying premise of a PRV proved appealing enough to lawmakers that a second PRV program was initiated for pediatric Rare Diseases in 2012, drawing a further parallel between the two underserved areas. The field was subsequently expanded to include a third PRV for material threat medical countermeasures (similar to EUNDS) in 2016.¹³⁹⁵ At the same time, the PRV risks becoming a victim of its own success; increasing the number of PRVs potentially available creates the danger that each individual PRV will be less commercially valuable, decreasing the incentive it creates.¹³⁹⁶ It also means companies seeking to earn a PRV by developing new drugs can pursue options other than Neglected Diseases to receive one; unfortunately, here too Neglected Diseases have proven less enticing to pharmaceutical companies than other areas like pediatric Rare Diseases.¹³⁹⁷ It is also difficult to determine to what extent the PRV has incentivized the actual development of novel drugs for Neglected Diseases. An early survey of pharmaceutical companies with existing programs for a PRV-eligible tropical disease – carried out before, among other things, a benchmark for the real-world

¹³⁹⁴ The possibility of a review being unsuccessful is not hypothetical. Novartis attempted to use the PRV it earned for the previously discussed antimalarial drug Coartem (artemether/lumefantrine) for an arthritis drug, but was unsuccessful. Hughes, Bethan, “Priority voucher flops” (2011) 29:11 *Nat Biotechnol* 958–958, online: <<http://www.nature.com/articles/nbt1111-958a>>.

¹³⁹⁵ Drugs to counter weaponized diseases like anthrax would be an example. *Food and Drug Administration Safety and Innovation Act*, Pub. L. No. 112-144, § 908, 126 Stat. 993, 1094 (2012); and *21st Century Cures Act*, Pub. L. No. 114-255, § 3086, 130 Stat. 1033, 1145 (2016).

¹³⁹⁶ Hamming, Lesley, “The Promise of Priority Review Vouchers as a Legislative Tool to Encourage Drugs for Neglected Diseases” (2013) 11 *Duke Law & Technology Review* 390–412.

¹³⁹⁷ United States Government Accountability Office, *Drug Development - FDA’s Priority Review Voucher Programs*, Report to Congressional Committees GAO-20-251 (2020).

market value of a PRV had been established – found the PRV was a consideration for most companies, but not the primary one.¹³⁹⁸ A later study looking at novel products to treat or cure NTDs found the proportion of NTD drugs among all products in development actually decreased in the first seven years of the PRV program compared with the preceding seven years; it concluded that the “priority review voucher was not associated with an increase in innovative, early-stage neglected tropical disease product development”.¹³⁹⁹ However, the impact of the PRV on driving initiatives that would not otherwise have occurred remains contentious; for instance, another study found that early-stage research had in fact increased for some Neglected Diseases, even if that early-stage research might not necessarily translate into marketed drugs.¹⁴⁰⁰ The most recent review, led by Ridley, the key original proponent of the PRV model, found that the PRV did have an effect, but was insufficient incentive on its own; it finds complementary “push” funding from non-profit organizations and similar bodies was necessary for early stage research.¹⁴⁰¹

The limited impact of the PRV on Neglected Diseases has also been reflected in approvals. Between the launch of the PRV and the addition of Chagas to the eligibility list in 2015, only three Neglected Disease PRVs had been awarded: Artemether/lumefantrine for treatment of malaria in 2008, bedaquiline for MDR-TB in 2012, and miltefosine for treatment of leishmaniasis in 2014.¹⁴⁰² There were warnings from the beginning. Kesselheim had written in 2008 that, in their existing form, “priority-review vouchers represent an inefficient and potentially dangerous

¹³⁹⁸ Robertson, Andrew S et al., “The Impact of the US Priority Review Voucher on Private-Sector Investment in Global Health Research and Development” (2012) 6:8 PLoS Negl Trop Dis e1750, online: <<https://dx.plos.org/10.1371/journal.pntd.0001750>>.

¹³⁹⁹ Jain, Nina et al., “Association of the Priority Review Voucher With Neglected Tropical Disease Drug and Vaccine Development” (2017) 318:4 JAMA 388–389. <<https://dx.plos.org/10.1371/journal.pntd.0006695>>.

¹⁴⁰⁰ Kerr, Kirk W, Thomas C Henry & Kathleen L Miller, “Is the priority review voucher program stimulating new drug development for tropical diseases?” (2018) 12:8 PLoS Negl Trop Dis e0006695.

¹⁴⁰¹ Ridley, David B, Pranav Ganapathy & Hannah E Kettler, “US Tropical Disease Priority Review Vouchers: Lessons In Promoting Drug Development And Access: Article examines infectious disease drug and vaccine development.” (2021) 40:8 Health Affairs 1243–1251, online: <<http://www.healthaffairs.org/doi/10.1377/hlthaff.2020.02273>>.

¹⁴⁰² Berman, Jonathan & Tanya Radhakrishna, “The Tropical Disease Priority Review Voucher: A Game-Changer for Tropical Disease Products” (2017) 96:1 Am J Trop Med Hyg 11–13.

way of encouraging research into tropical diseases".¹⁴⁰³ He doubted that PRVs would efficiently stimulate research among large pharmaceutical companies in an area they traditionally largely ignored, or be particularly effective for the smaller companies that did such research but could not make use of the PRVs themselves. Furthermore:

Another source of inefficiency is that a voucher's value will bear no relation to the usefulness of the drug whose development it is intended to reward. For example, the law stipulates that no voucher will be earned for a product whose "active ingredient" was previously approved. As a result, an effective novel antimalarial drug that degrades in the heat and must be taken six times a day would earn its sponsor a voucher, but no voucher would be granted for a follow-on formulation that might be more useful in resource-poor settings. Even more problematically, a sponsor rewarded with a voucher for FDA approval of a product for a neglected disease will have no incentive to follow through with implementation of the therapy.¹⁴⁰⁴

These are serious concerns that remain unresolved. Capturing less attention at the outset, however, was the fact that the PRV could be used to reward "innovations" involving virtually no innovation at all. Of the initial three drugs rewarded with a PRV for Tropical Diseases, only bedaquiline could readily be considered novel (and even here, a recent analysis suggests that public sector investment in its development considerably exceeded that by the pharmaceutical company that reaped its rewards).¹⁴⁰⁵ The other two initial PRV recipients could hardly be

¹⁴⁰³ Kesselheim, Aaron S, "Drug Development for Neglected Diseases — The Trouble with FDA Review Vouchers" (2008) 359:19 N Engl J Med 1981–1983, online: <<http://www.nejm.org/doi/abs/10.1056/NEJMp0806684>>.

¹⁴⁰⁴ Kesselheim, Aaron S, "Drug Development for Neglected Diseases — The Trouble with FDA Review Vouchers" (2008) 359:19 N Engl J Med 1981–1983, online: <<http://www.nejm.org/doi/abs/10.1056/NEJMp0806684>>.

¹⁴⁰⁵ Gotham, Dzintars et al., "Public investments in the clinical development of bedaquiline" (2020) 15:9 PLoS One e0239118. Ongoing access barriers include the fact it has only been registered in a small number of countries. Masini, Tiziana et al., "Will regulatory issues continue to be a major

considered innovative at all; both artemether/lumefantrine (discussed earlier) and miltefosine (revisited later) had already been in use elsewhere in the world for over a decade. Both were also already on the WHO MEML before they received US FDA approval. Indeed, artemether/lumefantrine was registered in 85 countries by that time; what is more, Novartis indicated it had already planned to bring the drug to the American market before the PRV was created.¹⁴⁰⁶ Given their demonstrated importance internationally well before the award of a PRV, these drugs showed early on that the system could be exploited by bringing a pre-existing Essential Medicine for a Neglected Disease to the US market. This should not have been a huge surprise in the first place; after all, similar issues had arisen with Essential Medicines for Neglected Diseases under the *Orphan Drug Act* years before. Despite that precedent, however, the PRV was not designed with measures to prevent this from occurring.

Under such circumstances, it is not so surprising that once Chagas was added to the list of eligible diseases in 2015, a company attempted to obtain FDA approval for benznidazole as a means to collect a potentially very lucrative PRV. As noted above, a further bonus of approval for benznidazole via this channel, alongside the PRV itself, would be the enforceable five-year monopoly over an off-patent drug. Previously, this monopoly had been a mere perk alongside the value of the PRV; after all, the PRV is targeted at diseases with “no significant market in developed nations”.¹⁴⁰⁷ However, by late 2015, the potential value of a *de facto* monopoly over an off-patent Essential Medicine for a Neglected Disease impacting small but vulnerable populations in the United States had been very publicly demonstrated; a *de jure* exclusivity would heighten the possibility for trolling off-patent drugs. And who better – or terrible enough – to exploit this loophole than Martin Shkreli? This is precisely what he attempted to do in 2015, shortly after

barrier to access to bedaquiline and delamanid?” (2018) 51:3 Eur Respir J 1702480, online: <<http://erj.ersjournals.com/lookup/doi/10.1183/13993003.02480-2017>>.

¹⁴⁰⁶ Anderson, Tatum, “Novartis under fire for accepting new reward for old drug” (2009) 373:9673 The Lancet 1414, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673609608047>>.

¹⁴⁰⁷ *Food, Drug & Cosmetic Act* 21 U.S.C. ch. 9 § 301 s. 524(a)(3)(R).

gaining a controlling stake in another small pharma company, KaloBios, and being named its Chairman and CEO.¹⁴⁰⁸

Shkreli's plan for benznidazole, as revealed in KaloBios documents submitted to the U.S. Securities and Exchange Commission (SEC), was one with potentially serious implications for access. A presentation for investors highlights the fact that "Benznidazole is the standard of care for Chagas Disease, is unavailable in the U.S., and eligible for a Priority Review Voucher upon approval".¹⁴⁰⁹ It explicitly outlines the goal of exploiting FDA mechanisms for very little work: "FDA minutes reflect our expectation that no Chagas clinical trials will be required".¹⁴¹⁰ Most disturbingly, it states "Pricing is expected to be similar to Hepatitis C antivirals".¹⁴¹¹ In 2013, Gilead had notoriously introduced sofosbuvir (trade name Sovaldi) at a list price of \$84,000USD for a 12 week course of treatment.¹⁴¹² This pricing was highly controversial.¹⁴¹³ At the same time, it must be emphasized that sofosbuvir was a genuine breakthrough in hepatitis C treatment; benznidazole was a drug that had been the global standard of care for decades.¹⁴¹⁴ As such, only the former could even claim to be reaping the just rewards of innovation.

¹⁴⁰⁸ KaloBios Pharmaceuticals, *KaloBios Pharmaceuticals [Presentation]* (US SEC copy, 2015), online: <https://www.sec.gov/Archives/edgar/data/1293310/000110465915082792/a15-24519_1ex99d1.htm> at slide 3.

¹⁴⁰⁹ KaloBios Pharmaceuticals, *KaloBios Pharmaceuticals [Presentation]* (US SEC copy, 2015), online: <https://www.sec.gov/Archives/edgar/data/1293310/000110465915082792/a15-24519_1ex99d1.htm> at slide 3.

¹⁴¹⁰ KaloBios Pharmaceuticals, *KaloBios Pharmaceuticals [Presentation]* (US SEC copy, 2015), online: <https://www.sec.gov/Archives/edgar/data/1293310/000110465915082792/a15-24519_1ex99d1.htm> at slide 12.

¹⁴¹¹ KaloBios Pharmaceuticals, *KaloBios Pharmaceuticals [Presentation]* (US SEC copy, 2015), online: <https://www.sec.gov/Archives/edgar/data/1293310/000110465915082792/a15-24519_1ex99d1.htm> at slide 15.

¹⁴¹² Johnson, Carolyn Y & Brady Dennis, "How an \$84,000 drug got its price: 'Let's hold our position ... whatever the headlines'", *The Washington Post* (1 December 2015), online: <<https://www.washingtonpost.com/news/wonk/wp/2015/12/01/how-an-84000-drug-got-its-price-lets-hold-our-position-whatever-the-headlines/>>.

¹⁴¹³ See e.g., "The price of good health" (2014) 20:4 Nat Med 319.

¹⁴¹⁴ Sofosbuvir was added to the WHO MEML in 2015; unlike the drugs at the core of this thesis, it is still under patent in many countries. This is also an illustration of the 21st Century trend of including patented drugs on the WHO MEML.

The KaloBios deal to acquire rights around benznidazole was first reported in early December 2015.¹⁴¹⁵ By the middle of that month, Shkreli would be arrested for securities fraud, the beginning of his legal troubles.¹⁴¹⁶ Not only that, KaloBios fired Shkreli as CEO the day of his arrest.¹⁴¹⁷ Nonetheless, the deal moved forward in his absence. A copy of the subsequent Letter of Intent between KaloBios and Savant Neglected Diseases, LLC outlines a joint effort to commercialize benznidazole in the USA.¹⁴¹⁸ KaloBios would be the driving force, but Savant would retain certain rights. What remains unclear even from the Letter of Intent is precisely what “rights” Savant brought to the table in the first place. Media reporting around this story frequently framed it much like the fresh-in-mind Shkreli-led fiasco of pyrimethamine.¹⁴¹⁹ An important, underemphasized difference is that there was no existing set of domestic rights to take over for benznidazole, as at the time of the deal it was neither approved nor produced in the United States. The most telling clue, found in the KaloBios presentation, is that Savant had “made significant progress on NDA-enabling [New Drug Application] requirements,” suggesting it was this material that was of particular value.¹⁴²⁰

News that KaloBios – and by extension the already infamous Shkreli – were trying to gain FDA approval for benznidazole also kicked off something rather unusual: A race to receive approval for an unmarketed medicine for a Neglected Disease, decades after its invention. Rather than the result of some new-found interest in Chagas itself, this competing effort to bring benznidazole to market was a direct response to KaloBios and fears of what a Shkreli-inspired model might

¹⁴¹⁵ “Shkreli’s KaloBios buys Chagas disease drug rights, shares soar”, *Reuters* (3 December 2015), online: <<https://www.reuters.com/article/us-kalobios-drug-idUSKBN0TM31220151203>>.

¹⁴¹⁶ Rushe, Dominic, “Martin Shkreli arrested by FBI over hedge fund investigation”, *The Guardian* (17 December 2015), online: <<https://www.theguardian.com/us-news/2015/dec/17/martin-shkreli-arrested-by-fbi-over-hedge-fund-investigation>>.

¹⁴¹⁷ “KaloBios fires Shkreli as CEO” *Reuters* (17 December 2015), online: <<https://www.reuters.com/article/us-usa-crime-shkreli-idUSKBN0U41R720151221>>.

¹⁴¹⁸ KaloBios Pharmaceuticals Inc, *Letter of Intent from KaloBios to Savant regarding the proposed acquisition of assets related to benznidazole*. (22 February 2016), online: <https://www.sec.gov/Archives/edgar/data/1293310/000121465916013789/ex10_1.htm>.

¹⁴¹⁹ See e.g., “Shkreli’s KaloBios buys Chagas disease drug rights, shares soar”, *Reuters* (3 December 2015), online: <<https://www.reuters.com/article/us-kalobios-drug-idUSKBN0TM31220151203>>.

¹⁴²⁰ KaloBios Pharmaceuticals, *KaloBios Pharmaceuticals [Presentation]* (US SEC copy, 2015), online: <https://www.sec.gov/Archives/edgar/data/1293310/000110465915082792/a15-24519_1ex99d1.htm> at slide 12.

mean for affordable access.¹⁴²¹ At this point, it is worth underscoring that any commercialization was going to increase the price for American patients (or at least their insurers), given benznidazole was then being provided at no cost via the CDC Drug Service formulary.¹⁴²² Nonetheless, few parties were likely to be as enthusiastic about exploiting a monopoly to its fullest extent as KaloBios.

The other contender was the Spanish company Chemo Research, S.L. (Chemo). In this race, it partnered with the non-profit Drugs for Neglected Diseases Initiative (DNDi), who “supported U.S. registration through provision of technical expertise and sharing of data from DNDi-led clinical trials”.¹⁴²³ In exchange for their support, part of the DNDi agreement with Chemo ensured “a substantial part of any revenue derived from the future sale of the PRV will be directed towards enhancing access to treatment for Chagas patients and improving patient health in other disease areas”.¹⁴²⁴ Ultimately, Chemo was first to the chequered flag; in August of 2017, the FDA granted approval for benznidazole to Chemo.¹⁴²⁵ Following its approval, the CDC discontinued its own benznidazole program via its formulary, and Chemo (now renamed Insud Pharma) began to commercially distribute the product via a subsidiary, Exeltis USA.¹⁴²⁶ Benznidazole for the US market now comes via two Spanish plants, with one (Química Sintética) producing the API and the other (Licónsa CMO) making benznidazole tablets.¹⁴²⁷ For KaloBios,

¹⁴²¹ Hernandez, Daisy, “A New Strategy to Undermine Big Pharma’s Price Gouging Actually Worked”, *Slate* (7 September 2017), online: <<https://slate.com/technology/2017/09/inside-the-battle-to-approve-a-chagas-treatment.html>>.

¹⁴²² Alpern, Jonathan D, Rogelio Lopez-Velez & William M Stauffer. “Access to benznidazole for Chagas disease in the United States—Cautious optimism?” (2017) 11:9 *PLoS Negl Trop Dis* e0005794, online: <<https://dx.plos.org/10.1371/journal.pntd.0005794>>.

¹⁴²³ Drugs for Neglected Diseases Initiative, “U.S. FDA approves Chemo Group’s benznidazole to treat children with Chagas disease”, (31 August 2017), online: <<https://dndi.org/press-releases/2017/fda-approves-benznidazole-chagas-children/>>.

¹⁴²⁴ Drugs for Neglected Diseases Initiative, “U.S. FDA approves Chemo Group’s benznidazole to treat children with Chagas disease”, (31 August 2017), online: <<https://dndi.org/press-releases/2017/fda-approves-benznidazole-chagas-children/>>.

¹⁴²⁵ US Food and Drug Administration, “Press Release - FDA approves first U.S. treatment for Chagas disease”, (29 August 2017), online: <<https://www.fda.gov/news-events/press-announcements/fda-approves-first-us-treatment-chagas-disease>>.

¹⁴²⁶ Yoshioka, Kota et al., “Access to Chagas disease treatment in the United States after the regulatory approval of benznidazole” (2020) 14:6 *PLoS Negl Trop Dis* e0008398, online: <<https://dx.plos.org/10.1371/journal.pntd.0008398>>.

¹⁴²⁷ Yoshioka, Kota et al., “Access to Chagas disease treatment in the United States after the regulatory approval of benznidazole” (2020) 14:6 *PLoS Negl Trop Dis* e0008398, online:

this was not merely a defeat but a disaster, with its stock dropping 73%.¹⁴²⁸ As of this writing, the company (now renamed Humanigen) is engaged in litigation against Savant Neglected Diseases, its partners in the FDA approval process.¹⁴²⁹

So what has happened with benznidazole in the United States following market entry nearly half a century after its creation? One study examining whether commercialization led to changes in access found that the monthly average of patients “increased from just under 5 persons during the period in which CDC provided benznidazole, to 13 on average in the nine months following commercialization on May 14, 2018”.¹⁴³⁰ It notes that this number remains small compared to the need for access to the drug; Exeltis had forecast demand at 200 patients per year.¹⁴³¹ It also notes that, despite approval only being for pediatric use, more than 90% of patients being treated both before and after approval were adults.¹⁴³² This highlights once again the important role of off-label prescribing in the context of Neglected Diseases, underscoring the value of formal market approval for enabling this practice. At the same time, it must be recognized that in at least one case, the authors of the study noted it was being given to an elderly patient (for a long time, the drug was not recommended for use in older adults, although evidence has evolved in recent years) and without confirmation of

<<https://dx.plos.org/10.1371/journal.pntd.0008398>>. Interestingly, despite production occurring in Spain, the drug is not yet registered there. Instead, use of this unapproved drug must be authorized by the Spanish Agency of Medicines and Medical Devices (AEMPS). Navarro, Miriam et al., “Estimating chagas disease prevalence and number of underdiagnosed, and undertreated individuals in Spain” (2022) 47 Travel Medicine and Infectious Disease 102284, online: <<https://linkinghub.elsevier.com/retrieve/pii/S1477893922000308>>.

¹⁴²⁸ Carroll, John, “A nonprofit group’s Chagas drug beat out Martin Shkreli’s old rival to FDA OK, valuable PRV”, *Endpoints News* (29 August 2017), online: <<https://endpts.com/fda-oks-nonprofit-groups-old-chagas-drug-handing-out-prv-and-clearing-way-to-cheap-price/>>.

¹⁴²⁹ A summary judgement on preliminary matters highlights some of these issues. *Humanigen, Inc. v. Savant Neglected Diseases, LLC* C.A. N17C-07-068-PRW CCLD (Del. Super. Ct. Aug. 17, 2020).

¹⁴³⁰ Yoshioka, Kota et al., “Access to Chagas disease treatment in the United States after the regulatory approval of benznidazole” (2020) 14:6 PLoS Negl Trop Dis e0008398, online: <<https://dx.plos.org/10.1371/journal.pntd.0008398>>.

¹⁴³¹ Yoshioka, Kota et al., “Access to Chagas disease treatment in the United States after the regulatory approval of benznidazole” (2020) 14:6 PLoS Negl Trop Dis e0008398, online: <<https://dx.plos.org/10.1371/journal.pntd.0008398>>.

¹⁴³² Yoshioka, Kota et al., “Access to Chagas disease treatment in the United States after the regulatory approval of benznidazole” (2020) 14:6 PLoS Negl Trop Dis e0008398, online: <<https://dx.plos.org/10.1371/journal.pntd.0008398>>.

diagnosis.¹⁴³³ This is itself a reminder that physicians are themselves not infallible in their prescribing choices. However, in a positive outcome, the study did not find price to be a major barrier to access, despite the fact it was no longer provided for free by the CDC.¹⁴³⁴ This echoes efforts made to use the proceeds of the PRV to support affordable access.¹⁴³⁵ Together, the evidence thus far supports the notion that it is possible to bring such a drug to market, improving access while selling it at a reasonable price. However, it still does not clarify a baseline of what incentives would be needed – short of the potentially nine-figure Shkreli-luring financial inducement of a PRV, or a fevered bid to stop him – to bring such a drug to market after being largely ignored for over forty years, particularly without the involvement of a non-profit like DNDi.

Nifurtimox and the PRV reforms

One side effect of benznidazole on the legal rather than medical side is that it finally led to the enactment of reforms to the PRV program. For this, perhaps Martin Shkreli deserves some credit, albeit indirectly. In the wake of the high-profile race for benznidazole approval, changes were made to the tropical diseases PRV as part of the *FDA Reauthorization Act* of 2017 (the same legislation that also introduced the sole-source drug competition measures discussed earlier).¹⁴³⁶ To prevent total free riding on pre-existing drugs, applications submitted after September 30, 2017 must now contain reports of one or more new clinical investigations (other than bioavailability studies) that are essential to the approval of the application and conducted or sponsored by the applicant.¹⁴³⁷ In addition, the applicant must provide an attestation that such report(s) were not submitted as part of an

¹⁴³³ Yoshioka, Kota et al., “Access to Chagas disease treatment in the United States after the regulatory approval of benznidazole” (2020) 14:6 PLoS Negl Trop Dis e0008398, online: <<https://dx.plos.org/10.1371/journal.pntd.0008398>>; for more on evolving approaches to treatment see Viotti, R et al., “Towards a paradigm shift in the treatment of chronic Chagas disease” (2014) 58:2 Antimicrob Agents Chemother 635–639.

¹⁴³⁴ Yoshioka, Kota et al., “Access to Chagas disease treatment in the United States after the regulatory approval of benznidazole” (2020) 14:6 PLoS Negl Trop Dis e0008398, online: <<https://dx.plos.org/10.1371/journal.pntd.0008398>>.

¹⁴³⁵ Bern, Caryn et al., “Chagas Disease in the United States: a Public Health Approach” (2019) 33:1 Clin Microbiol Rev, online: <<https://journals.asm.org/doi/10.1128/CMR.00023-19>>.

¹⁴³⁶ *FDA Reauthorization Act of 2017* (FDARA, P.L. 115-52), sec. 611.

¹⁴³⁷ *FDA Reauthorization Act of 2017* (FDARA, P.L. 115-52), sec. 611.

application for marketing approval or licensure by a regulatory authority in India, Brazil, Thailand, or any of the numerous countries (including Canada) that was a member of the Pharmaceutical Inspection Convention or the Pharmaceutical Inspection Cooperation Scheme prior to September 27, 2007.¹⁴³⁸ Given the intended goal of the PRV is innovation, the addition of these restrictions only raises further questions about why similar rules were not included from the beginning.

Nevertheless, even in the wake of reforms to the PRV, it appears the reward is still great enough that some companies have been willing to take the additional step of conducting some further research on an existing Essential Medicine to justify eligibility for a Tropical Disease PRV. This is no longer total free riding, though it remains unclear whether the reward is commensurate with the added benefit of this research. Benznidazole, as will be recalled, is not the only longstanding Chagas disease treatment to have received a PRV since the disease became eligible. The other, however, has received considerably less attention, presumably at least partially attributable to the lack of a connection to Martin Shkreli. In August of 2020, a letter from the FDA confirmed that Bayer had been granted a tropical disease PRV for nifurtimox, a drug Bayer itself had developed over fifty years earlier.¹⁴³⁹

The nifurtimox story also ties directly into another tale told earlier in this thesis. Nifurtimox was originally developed by Bayer in the 1960s and marketed in several Latin American countries under the tradename Lampit. It has been on the WHO MEML for the treatment of Chagas disease since the inaugural list in 1977. However, Bayer never sought approval in the USA. Then, in 1997, Bayer made the commercial decision to stop producing the drug entirely. This had repercussions for more than one Neglected Disease; nifurtimox is also used to treat African trypanosomiasis, and Bayer's actions around both it and fellow sleeping sickness

¹⁴³⁸ *FDA Reauthorization Act of 2017* (FDARA, P.L. 115-52), sec. 611.

¹⁴³⁹ Farley, John J, [Letter to Bayer Pharmaceuticals re: Nifurtimox] (US FDA, 2020), online: <https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/213464Orig1s000ltr.pdf>.

Essential Medicine suramin have been explored earlier in this thesis.¹⁴⁴⁰ Following pushback, as previously discussed, Bayer made an agreement with the WHO to resume production and donate the drug to WHO programs.¹⁴⁴¹ Thus, unlike KaloBios and the race for benznidazole, Bayer's bid for a PRV involved finally taking action on a drug it innovated half a century ago and has – barring the low point in the late 1990s and early 2000s – manufactured ever since. Today, it is manufactured by Bayer HealthCare in El Salvador.¹⁴⁴² It nonetheless seemingly took the incentive of a PRV to finally get this large, longstanding originator company to bring one of its Essential Medicines to market in the world's largest market for pharmaceuticals. Once again, it is unclear how large the gap is between the size of the incentive actually received by Bayer for finally bringing nifurtimox to the US market, and the size of the incentive that would have tipped the balance for it to do so.

Bayer is not the only company who refrained from bringing an Essential Medicine for a Neglected Disease to market, only to earn a PRV for finally doing so decades later. Another such drug would sneak onto the American market just under the wire before the post-benznidazole requirements came into effect. Triclabendazole was developed as a veterinary drug in the 1980s and has been on the WHO MEML since 1997 for the treatment of fascioliasis and paragonimiasis, two parasitic Neglected Diseases cause by flatworms. It has been donated to the WHO for use in low-income endemic countries by Novartis since the mid-2000s.¹⁴⁴³

¹⁴⁴⁰ See e.g., Etchegorry, M Gastellu et al., "Availability and affordability of treatment for Human African Trypanosomiasis" (2001) 6:11 Trop Med Int Health 957–959, online: <<http://doi.wiley.com/10.1046/j.1365-3156.2001.00764.x>>.

¹⁴⁴¹ Alpern, Jonathan D, Rogelio Lopez-Velez & William M Stauffer. "Access to benznidazole for Chagas disease in the United States—Cautious optimism?" (2017) 11:9 PLoS Negl Trop Dis e0005794, online: <<https://dx.plos.org/10.1371/journal.pntd.0005794>>. However, it should be noted that this donation program has created its own questions in various settings; for instance, donations of nifurtimox meant it was far more likely to be used in Mexico than benznidazole, which was not donated, even though neither drug was formally registered. See e.g., Manne, Jennifer M et al. "Barriers to Treatment Access for Chagas Disease in Mexico" (2013) 7:10 PLoS Negl Trop Dis e2488, online: <<https://dx.plos.org/10.1371/journal.pntd.0002488>>.

¹⁴⁴² Manne, Jennifer M et al. "Barriers to Treatment Access for Chagas Disease in Mexico" (2013) 7:10 PLoS Negl Trop Dis e2488, online: <<https://dx.plos.org/10.1371/journal.pntd.0002488>>.

¹⁴⁴³ Gandhi, Preetam et al., "Triclabendazole in the treatment of human fascioliasis: a review" (2019) 113:12 Transactions of The Royal Society of Tropical Medicine and Hygiene 797–804, online: <<https://academic.oup.com/trstmh/article/113/12/797/5602280>>.

Prior to its approval, it was also a first-line treatment recommended by the CDC, despite its lack of formal availability.¹⁴⁴⁴ The PRV, and FDA approval, are only for fascioliasis; however, its formal market presence enables off-label use for other conditions like paragonimiasis. While Novartis was not awarded the PRV until 2019, the first portion of their submission was made in late September 2017, just days before the reforms came into effect.¹⁴⁴⁵ As a result, Novartis claimed its second PRV for a widely used Essential Medicine for a Neglected Disease from its own portfolio that it had not previously sought approval for in the USA, following artemether/lumefantrine.¹⁴⁴⁶

At the same time, while nifurtimox received a PRV after reforms to the PRV system, not all applications for pre-existing Essential Medicines since that time have met with similar success. Amazingly, the post-benznidazole changes appear to have impacted a second race for a PRV, this time for parenteral artesunate, an important artemisinin derivative found on the WHO MEML and discussed earlier in this thesis. It too had previously only been available through the CDC Drug Service formulary as an investigational new drug. The two companies in the race for the PRV were Amivas LLC and La Jolla Pharmaceutical Company. In 2020, Amivas' application to market parenteral artesunate was approved by the US FDA; it came to market in 2021.¹⁴⁴⁷ The approval letter, however, is silent on the issue of a PRV.¹⁴⁴⁸ In an interview about the approval, the Chief Medical Officer of the company stated "Amivas did request a priority review voucher and we believe that

¹⁴⁴⁴ Graham, Camilla S, Sharon B Brodie & Peter F Weller, "Imported *Fasciola hepatica* Infection in the United States and Treatment with Triclabendazole" (2001) 33:1 Clin Infect Dis 1–5, online: <<https://academic.oup.com/cid/article-lookup/doi/10.1086/320870>>.

¹⁴⁴⁵ Fox, Edward, [Letter to Novartis Pharmaceuticals re: Egaten (triclabendazole)] (US FDA, 2020), online: <https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2019/208711Orig1s000ltr.pdf>; Médecins Sans Frontières, "Novartis secures FDA innovation prize for 30-year-old drug" (20 February 2019), online: <<https://www.doctorswithoutborders.org/what-we-do/news-stories/news/novartis-secures-fda-innovation-prize-30-year-old-drug>>.

¹⁴⁴⁶ Like artemether/lumefantrine, triclabendazole has never been submitted for market approval in Canada.

¹⁴⁴⁷ Amivas (US) LLC, "Amivas (US), LLC Announces U.S. Launch of Artesunate for Injection for Initial Treatment of Severe Malaria", (30 March 2021), online: <<https://www.prnewswire.com/news-releases/amivas-us-llc-announces-us-launch-of-artesunate-for-injection-for-initial-treatment-of-severe-malaria-301258501.html>>.

¹⁴⁴⁸ Farley, John J, [Letter to Amivas LLC re: Artesunate] (US FDA, 2020).

we have met all the statutory requirements in order for us to be granted one. It is our understanding that at present, it is still with the FDA and they are still considering the merits of that matter and will revert back to us soon".¹⁴⁴⁹ As of this writing, however, the FDA, somewhat oddly, has made no public announcement definitively clarifying the status of this Tropical Disease PRV.

In the interim, commentators have linked this failure to award a PRV with a serious issue that has arisen following approval: a massive increase in price.¹⁴⁵⁰ Rather than being provided for free via the CDC Drug Service, or for tens of dollars in some African countries, a course of artesunate treatment in the United States now has a price tag of roughly \$30,000USD; commentators allege that this high price is the consequence of not receiving a PRV, which would purportedly have led to a less egregious price.¹⁴⁵¹ While it is of course possible the award of a PRV might have led to a lower price, answers to the question of how much of the PRV would actually have been passed on as savings to the ultimate payer remain speculative. Unlike benznidazole, there is no evidence of an agreement with a non-profit organization over what to do with the PRV proceeds that would help govern future pricing. It also remains unclear what costs were actually incurred in bringing this pre-existing Essential Medicine to market, even after the 2017 PRV reforms. As noted earlier, this higher price has already impacted Canada, which formerly obtained its supply through the SAP solely from the US but has now shifted towards also drawing upon a WHO Prequalified source from China.

As for the losing company in the race for approval, La Jolla had highlighted the importance of receiving a Tropical Disease PRV in its own filings with the US

¹⁴⁴⁹ Mezher, Michael, "FDA approves IV artesunate for severe malaria", *Regulatory Focus* (28 May 2020), online: <<https://www.raps.org/news-and-articles/news-articles/2020/5/fda-approves-iv-artesunate-for-severe-malaria>>.

¹⁴⁵⁰ Frosch, Anne EP, Aileen Ahiskali & Chandy C John, "Unaffordable treatment for severe malaria highlights U.S. drug market pitfalls", *STAT News* (11 June 2021), online: <<https://www.statnews.com/2021/06/11/unaffordable-treatment-for-severe-malaria-highlights-u-s-drug-market-pitfalls/>>.

¹⁴⁵¹ Frosch, Anne EP, Aileen Ahiskali & Chandy C John, "Unaffordable treatment for severe malaria highlights U.S. drug market pitfalls", *STAT News* (11 June 2021), online: <<https://www.statnews.com/2021/06/11/unaffordable-treatment-for-severe-malaria-highlights-u-s-drug-market-pitfalls/>>.

Securities and Exchange Commission.¹⁴⁵² It saw its stock tumble 20%.¹⁴⁵³ This, together with the even greater stock decline seen by KaloBios, underscores a further downside of a PRV model for bringing existing Essential Medicines to market: Quite aside from the question of the PRV fueling less than altruistic motives, some of the companies attracted by the financial prospect of a transferable PRV for a pre-existing drug may simply not be in the most stable position to provide a sustainable long-term supply of an Essential Medicine. As the Chao Center illustrates, a small company – even one with goals that are not purely commercial – that only makes one old drug for a small market may itself not be sustainable, certainly in comparison to a major pharmaceutical company with an extensive product catalogue. At the same time, while tougher standards for the Tropical Disease PRV make it harder to free-ride on approval of an old drug, this does not address the fact that this pathway seems to be the only reason some Essential Medicines for Neglected Diseases have entered the American market at all.¹⁴⁵⁴

Unresolved issues with the PRV

By the end of April 2022, 13 of the 53 PRVs awarded across all three categories had been for tropical diseases.¹⁴⁵⁵ At the best of times, it would be hard to describe

¹⁴⁵² La Jolla Pharmaceutical Company, *Form 10-K for the fiscal year ended December 31, 2019* (United States Securities and Exchange Commission, 2020), online: <<https://www.sec.gov/Archives/edgar/data/920465/000092046520000036/ljpc-201910xk.htm>>.

¹⁴⁵³ “La Jolla feels the burn of rival malaria approval”, *Endpoints News* (27 May 2020), online: <<https://endpts.com/la-jolla-feels-the-burn-of-rival-malaria-approval-with-another-10b-bayer-could-finally-weed-out-its-herbicide-problem/>>.

¹⁴⁵⁴ The revisions to the Tropical Diseases PRV have had further implications, including for other PRV programs. In October of 2020, amidst hype about another of their products being used to treat Donald Trump during his COVID-19 hospitalization, the pharmaceutical company Regeneron received FDA approval for Inmazeb, the first treatment of Ebola virus disease. However, its application for a Tropical Disease PRV was turned down on the grounds of not including a new clinical investigation it had conducted or sponsored. Nonetheless, at the same time, Regeneron did receive a Material Threat Medical Countermeasure PRV for the same drug. Farley, John J, [*Letter to Regeneron Pharmaceuticals re: Inmazeb*] (US FDA, 2020). As such, while tightening standards for the Tropical Disease PRV has made it harder to simply dust off an old drug and register it in the US in exchange for a Tropical Disease PRV, it did not close the door to receipt of a different PRV for the same drug.

¹⁴⁵⁵ Ridley, David B. Priority Review Vouchers (Website). Durham (NC): Duke University Fuqua School of Business, online: <<https://sites.fuqua.duke.edu/priorityreviewvoucher>>. Accessed May 1, 2022.

thirteen products over as many years as an unbridled triumph for Neglected Disease research. This is all the more the case when one considers the dearth of scientific innovation involved. Of these thirteen, three are novel vaccines; three others are drugs not currently found on the WHO MEML.¹⁴⁵⁶ The remaining seven drugs are Essential Medicines, six of which were already on the WHO MEML before they received a PRV.¹⁴⁵⁷ These outcomes can be seen in **Table 3**.¹⁴⁵⁸

¹⁴⁵⁶ These three are moxidectin, pretomanid, tafenoquine. Based on updated WHO guidance to treatment of DR-TB released in May 2022, this author would wager pretomanid will be added to the next edition of the WHO MEML. World Health Organization, "Rapid communication: Key changes to the treatment of drug-resistant tuberculosis" (2 May 2022). Online: <<https://www.who.int/publications/i/item/WHO-UCN-TB-2022-2>>.

¹⁴⁵⁷ The only exception is bedaquiline.

¹⁴⁵⁸ PRV data in this table is extrapolated from the Priority Review Vouchers website maintained by David Ridley (online: <<https://sites.fuqua.duke.edu/priorityreviewvoucher/>>), which deserves full credit for being the most user-friendly source for this information, and cross-checked with FDA sources for confirmation.

Table 3: Drugs approved in the USA via the Tropical Disease PRV

Drug name/ (trade name)	PRV Indication	Drug Company	WHO MEML?	Year of PRV
artemether + lumefantrine (Coartem)	Treatment of acute, uncomplicated malaria infection	Novartis	Yes (2002)	2009
bedaquiline (Sirturo)	Treatment of MDR- TB	Janssen	Yes (2015)	2012
miltefosine (Impavido)	Treatment of leishmaniasis	Knight Therapeutics	Yes (2011)	2014
(Vaxchora Pax)	Cholera vaccine	Vax Bermuda Ltd.	*Sort of (2007) (MEML simply says "cholera vaccine")	2016
benznidazole	Treatment of Chagas disease	Chemo Research S.L. /DNDi	Yes (1987)	2017
moxidectin	Treatment of onchocerciasis, (river blindness)	Medicines Development for Global Health	No	2018
tafenoquine (Krintafel)	To prevent relapse of Plasmodium vivax malaria	GlaxoSmithKline	No	2018
triclabendazole (Egaten)	Treatment of fascioliasis	Novartis	Yes (1997)	2019
(Dengvaxia)	Dengue vaccine	Sanofi	Yes (2019)	2019
pretomanid (Dovprela)	Treatment of MDR- TB	The Global Alliance for TB Drug Development (TB Alliance)	No	2019
rVSV-ZEBOV (Ervebo) vaccine	Ebola vaccine	Merck	No	2019
nifurtimox (Lampit)	Treatment of Chagas disease	Bayer	Yes (1977)	2020
fexinidazole	Treatment of sleeping sickness	DNDi/Sanofi	Yes (2019)	2021

There are a few observations to draw. One, echoing earlier analyses, is that the PRV is an underwhelming tool for promoting truly innovative drugs for Neglected Diseases. Nevertheless, one arguable success of the Tropical Disease PRV is that it may have provided the necessary leverage for non-profit organizations to bring drugs for Neglected Diseases to market. This has been touched on already with DNDi's involvement with benznidazole, but is also reflected in the development of further drugs. For instance, it has been argued that the PRV program was pivotal to the development and approval of moxidectin by the non-profit Medicines

Development for Global Health (MDGH).¹⁴⁵⁹ Moxidectin is not a novel compound; like ivermectin, it is a longstanding veterinary drug.¹⁴⁶⁰ However, research on human use had never progressed to approval of the drug in any jurisdiction. In a variation on the story oft repeated throughout this thesis, the pharmaceutical company Wyeth had partnered with the WHO in 2009 to conduct human trials.¹⁴⁶¹ Around the same time, however, Wyeth was bought out by Pfizer, who chose not to actively pursue the drug for human use.¹⁴⁶² MDGH ultimately moved forward by leveraging the PRV for an investment of \$13 million USD by the Global Health Investment Fund (GHIF), “making this the first social impact investment raised specifically on the potential value of a PRV”.¹⁴⁶³ Similarly, pretomanid, only the third novel TB drug in half a century, was developed by the non-profit TB Alliance; other global health NGOs have called upon TB Alliance to clarify its precise plans for its PRV (which as of this writing has not been used or transferred), but it has the potential to improve access or underwrite future innovations.¹⁴⁶⁴ And finally, any benefits accruing from the most recent Tropical Disease PRV, for the sleeping sickness drug fexinidazole, will be split between DNDi and the pharmaceutical

¹⁴⁵⁹ Olliaro, Piero L et al., “Creative use of the priority review voucher by public and not-for-profit actors delivers the first new FDA-approved treatment for river blindness in 20 years” (2018) 12:11 PLoS Negl Trop Dis e0006837.

¹⁴⁶⁰ Moxidectin is available in Canada for veterinary use from multiple companies and in a range of formulations.

¹⁴⁶¹ “UN agency announces start of clinical trial for river blindness drug”, UN News (1 July 2009), online: <<https://news.un.org/en/story/2009/07/305272>>.

¹⁴⁶² Ridley, David B, Pranav Ganapathy & Hannah E Kettler, “US Tropical Disease Priority Review Vouchers: Lessons In Promoting Drug Development And Access: Article examines infectious disease drug and vaccine development.” (2021) 40:8 Health Affairs 1243–1251, online:

<<http://www.healthaffairs.org/doi/10.1377/hlthaff.2020.02273>>; Davies, Robin, “Really ending river blindness: Mark Sullivan and John Reeder”, (31 January 2020), online: *Dev Policy* <<https://devpolicy.org/aidprofiles/2020/01/31/really-ending-river-blindness-mark-sullivan-and-john-reeder/>>.

¹⁴⁶³ Olliaro, Piero L et al., “Creative use of the priority review voucher by public and not-for-profit actors delivers the first new FDA-approved treatment for river blindness in 20 years” (2018) 12:11 PLoS Negl Trop Dis e0006837.

¹⁴⁶⁴ Médecins Sans Frontières, “Promising new tuberculosis drug pretomanid approved, but will it be affordable?”, (15 August 2019), online: <<https://www.msf.org/promising-new-tuberculosis-drug-approved-will-it-be-affordable>>; Treatment Action Group, “TAG statement on FDA priority review of pretomanid”, (11 March 2019), online: <<https://www.tbonline.info/posts/2019/3/11/tag-statement-fda-priority-review-pretomanid/>>. It is worth noting that the underlying patent for pretomanid has also expired.

company Sanofi.¹⁴⁶⁵ While there are relatively few examples to draw upon, those that do exist suggest that the financial leverage the PRV can offer non-profit developers of innovative drugs for Neglected Diseases should not be dismissed offhand; in turn, the participation of non-profit entities like DNDi in market applications may help mitigate risks that an approved drug will be inaccessible to patients. However, even this smattering of success stories is not enough to suggest the PRV is the solution to reviving innovation for Neglected Diseases.

All this said, the fact that the PRV is ineffective at achieving its goal of encouraging the development of genuinely novel drugs for Neglected Diseases should not totally obscure the fact it has been slightly more effective, albeit unintentionally, at encouraging the market entry of existing Essential Medicines. This is particularly obvious in the case of originator companies finally bringing their drugs to market decades after the fact. Indeed, even the post-benznidazole reforms do not appear to have stemmed the tide of old Essential Medicines such as nifurtimox being brought to market. As such, the question must be asked: Rather than being seen as an inadvertent side-effect underscoring the failure of the PRV to effectively promote genuine innovation, should bringing old Essential Medicines to market be accepted as an appropriate end goal?

After all, some of these drugs had languished in limbo for decades, recognized (and employed) as the standard of care, but never formally available in the United States. In a regulatory system where approval is dependent on market interest rather than medical value, some of the ideas underpinning the PRV – such as redirecting the value of a PRV towards a more lucrative drug – are fairly clever. Furthermore, while the author sympathizes with the view that companies should not unjustly reap the rewards of bringing to market drugs they either did not develop, or developed decades ago but never bothered to bring to market everywhere they were needed, this must be pragmatically balanced against the advantages of making these drugs formally available now. Given the value of the

¹⁴⁶⁵ Drugs for Neglected Diseases initiative, “US FDA approves fexinidazole as the first all-oral treatment for sleeping sickness”, (19 July 2021), online: <<https://dndi.org/press-releases/2021/us-fda-approves-fexinidazole-as-first-all-oral-treatment-sleeping-sickness/>>.

PRV is itself tied to the market, the direct financial cost to the state (and, by extension, the taxpayer) is minimal. A system in which the company reaps a reward such as a PRV price set by the market, as opposed to exacting an extortionate price for the drug itself, may not actually be an unreasonable approach.

In support of this idea, compare the relative (rather than absolute) success of the PRV in bringing Neglected Disease drugs to market in the United States with the fate of those same drugs in Canada, where not a single drug or vaccine awarded a Tropical Medicine PRV has ever been brought to market. This is despite the fact that moxidectin is widely available in Canada as a veterinary drug, and the novel Ebola virus vaccine Ervebo was actually developed not merely in Canada, but at the publicly owned National Microbiology Lab in Winnipeg.¹⁴⁶⁶ At the same time, as the story of miltefosine shows, initiatives like the PRV in their current form are still insufficient to ensure affordable access, even if they were to openly embrace existing medicines as their primary target.

Miltefosine: The PRV with the Canadian Connection

There is a Canadian connection to the clearest demonstration that an Essential Medicine for a Neglected Disease cannot be simply assumed to become more affordable or accessible following receipt of a PRV under the current system, and by extension why the PRV model should not itself be imported wholesale. The Essential Medicine miltefosine is used to treat leishmaniasis, a parasitic disease whose annual death toll is second only to malaria.¹⁴⁶⁷ Sandflies are the vector of the protozoic leishmania parasite, which manifests in three main forms: cutaneous, mucocutaneous, and the most serious, visceral (also known as kala-azar). In 2014, as noted earlier, miltefosine became the third drug to receive a tropical disease

¹⁴⁶⁶ The failures encountered getting this vaccine out of the lab and into patients will not be recounted here, but see Herder, Matthew, Janice E Graham & Richard Gold, "From discovery to delivery: public sector development of the rVSV-ZEBOV Ebola vaccine" (2020) *Journal of Law and the Biosciences* 19, online: <<https://academic.oup.com/jlb/advance-article/doi/10.1093/jlb/lz019/5706941>>. For a slightly different view, see Attaran, Amir & Jason W Nickerson, "Is Canada patent deal obstructing Ebola vaccine development?" (2014) 384:9958 *The Lancet* e61, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673614620444>>.

¹⁴⁶⁷ DebRoy, Swati et al., "Challenges in modeling complexity of neglected tropical diseases: a review of dynamics of visceral leishmaniasis in resource limited settings" (2017) 14 *Emerg Themes Epidemiol* 10.

PRV from the US FDA. Miltefosine is also historically noteworthy as the first drug whose PRV was sold on the open market, fetching the sum of \$125 million USD, and thereby demonstrating the commercial value of the PRV as a saleable commodity.¹⁴⁶⁸ However, like so many of the medicines under discussion, it was not a new drug; developed as a cancer treatment in the 1980s, it was registered for leishmaniasis in India and Germany in 2004, and a number of South American countries in subsequent years.¹⁴⁶⁹ It was added to the WHO MEML three years before it received FDA approval.

Another noteworthy piece of the miltefosine story is that it was once heralded as a breakthrough in public-private partnerships for developing treatments for Neglected Diseases.¹⁴⁷⁰ Access *after* its development, however, has been notably less of a success, with the drug never becoming as affordable or widely available as hoped.¹⁴⁷¹ This was a concern well before the PRV entered the picture, though it would continue this same trajectory. One of the reasons early hopes were dashed is that initial steps intended to preserve widespread, affordable access unraveled as the rights to the drug changed hands. This is a cautionary tale for those who think an unenforceable arrangement, even between parties with the best of intentions, will be sufficient to ensure access. The original miltefosine partnership, between the WHO's Special Programme for Research and Training in Tropical Diseases and the pharmaceutical company Asta Medica, involved a memorandum of understanding with a framework for ensuring availability and affordability; the company retained control over private sector pricing, but would make it available at a preferential price (production cost plus a modest markup)

¹⁴⁶⁸ Berman, Jonathan, "Miltefosine, an FDA-approved drug for the 'orphan disease', leishmaniasis" (2015) 3:6 Expert Opinion on Orphan Drugs 727–735, online: <<http://www.tandfonline.com/doi/full/10.1517/21678707.2015.1039510>>.

¹⁴⁶⁹ Sunyoto, Temmy, Julien Potet & Marleen Boelaert, "Why miltefosine—a life-saving drug for leishmaniasis—is unavailable to people who need it the most" (2018) 3:3 BMJ Glob Health e000709, online: <<https://gh.bmj.com/lookup/doi/10.1136/bmjgh-2018-000709>>.

¹⁴⁷⁰ Gutteridge, WE, "TDR collaboration with the pharmaceutical industry" (2006) 100 Transactions of the Royal Society of Tropical Medicine and Hygiene S21–S25, online: <<https://academic.oup.com/trstmh/article-lookup/doi/10.1016/j.trstmh.2006.02.013>>.

¹⁴⁷¹ Sunyoto, Temmy, Julien Potet & Marleen Boelaert, "Why miltefosine—a life-saving drug for leishmaniasis—is unavailable to people who need it the most" (2018) 3:3 BMJ Glob Health e000709, online: <<https://gh.bmj.com/lookup/doi/10.1136/bmjgh-2018-000709>>.

within the public sector in all developing countries, “conditional on the free provision of the drug to patients”.¹⁴⁷²

However, as the drugs discussed in this thesis seem prone to do, the ownership of miltefosine promptly changed hands multiple times. This in turn caused changes in licencing agreements rendering that initial memorandum of understanding obsolete; as Sunyoto and colleagues outline, the original intentions between the WHO and Asta Medica could not be effectively enforced with that company’s successors.¹⁴⁷³ After a series of transfers, ownership of miltefosine, its tradename Impavido, and rights related to its manufacture, production, distribution, and marketing eventually made their way to the Canadian company Paladin Labs Inc., who acquired them from AEterna Zentaris in 2008 for \$9.125million (CDN).¹⁴⁷⁴

Shortly thereafter, as described in a rather fawning newspaper portrait, Paladin’s owner, Jonathan Goodman, sold Paladin to Endo Health Solutions Inc. The one asset he hung onto – and spun off into his new company – was miltefosine.¹⁴⁷⁵ As other news stories from the time explain, miltefosine was not itself the primary asset of his new company, Knight Therapeutics; the PRV associated with miltefosine’s US approval was.¹⁴⁷⁶ The sale of this PRV to Gilead brought in the

¹⁴⁷² Sunyoto, Temmy, Julien Potet & Marleen Boelaert, “Why miltefosine—a life-saving drug for leishmaniasis—is unavailable to people who need it the most” (2018) 3:3 BMJ Glob Health e000709, online: <<https://gh.bmj.com/lookup/doi/10.1136/bmjgh-2018-000709>>.

¹⁴⁷³ These multiple ownership changes are effectively presented in a graphic in the original article that is not reproduced here. Sunyoto, Temmy, Julien Potet & Marleen Boelaert, “Why miltefosine—a life-saving drug for leishmaniasis—is unavailable to people who need it the most” (2018) 3:3 BMJ Glob Health e000709, online: <<https://gh.bmj.com/lookup/doi/10.1136/bmjgh-2018-000709>>.

¹⁴⁷⁴ Paladin Labs & AEterna Zentaris, “AEterna Zentaris and Paladin Labs Inc. Complete Sale and Purchase of Miltefosine Rights”, (1 April 2008), online: <<https://www.biospace.com/article/releases/aeterna-zentaris-and-paladin-labs-inc-complete-sale-and-purchase-of-miltefosine-rights-/>>.

¹⁴⁷⁵ “‘If Canada was efficient, I wouldn’t exist.’ The miraculous success of Jonathan Ross Goodman”, *Financial Post* (31 July 2017), online: <<https://financialpost.com/investing/goodman-rallies-from-near-death-bike-spill-for-drug-renaissance>>.

¹⁴⁷⁶ Mullaly, Hogan, “Investors follow Paladin’s Goodman to Knight Therapeutics”, *Cantech Letter* (24 March 2014), online: <<https://www.cantechletter.com/2014/03/investors-like-paladins-goodman-betting-big-knight-therapeutics/>>; Zehr, Leonard, “Knight won’t rest til it bests Paladin”, *BioTuesdays* (13 May 2014), online: <<https://biotuesdays.com/2014/05/13/2014-5-13-knight-wont-rest-til-it-bests-paladin/>>.

aforementioned \$125 million USD.¹⁴⁷⁷ In a further sign of the weaknesses of the structure of the PRV program, Knight reaped this reward a year and a half before the drug actually entered the US market.¹⁴⁷⁸ Knight Therapeutics, based in Montréal, continues to hold the rights to Impavido. Knight has never attempted to market the drug in Canada. Thus we see a Canadian company profit from a US PRV for a drug developed by a German company working in India that was already on the WHO MEML and remains unavailable in its home country. This is particularly ironic given that Knight's broader business model is ostensibly acquiring marketing rights to specialty drugs in small markets.¹⁴⁷⁹ In many cases, these rights are for the Canadian market; in other words, Knight focuses on single-source, small market drugs in Canada. Knight's usual approach isn't an entirely cost-free process; as the *Financial Post* profile noted:

Even for a rubber stamp approval of a drug cleared by the U.S. Food & Drug Administration, reformatting the paperwork to Health Canada's requirements costs upward of \$500,000 and takes about six months. Companies then face about two more years to wend through the layers of bureaucracy.¹⁴⁸⁰

This highlights once more some of the commercial considerations facing companies that wish to enter the Canadian market for niche drugs, even where they will have a *de facto* monopoly that is unlikely to attract competition; in the case of miltefosine, it is evidently not of interest even to a company that already holds the rights

¹⁴⁷⁷ Knight Therapeutics Inc, "Press Release - Knight Sells Priority Review Voucher to Gilead", (19 November 2014), online: <<https://www.globenewswire.com/news-release/2014/11/19/1439078/0/en/Knight-Sells-Priority-Review-Voucher-to-Gilead.html>>.

¹⁴⁷⁸ Shahriar, Arman A & Jonathan D Alpern, "Antiparasitic Drugs in the United States—Two Roads to High Prices" (2020) 5 Front Sociol 540478, online: <<https://www.frontiersin.org/articles/10.3389/fsoc.2020.540478/full>>.

¹⁴⁷⁹ "If Canada was efficient, I wouldn't exist: The miraculous success of Jonathan Ross Goodman", *Financial Post* (31 July 2017), online: <<https://financialpost.com/investing/goodman-rallies-from-near-death-bike-spill-for-drug-renaissance>>.

¹⁴⁸⁰ "If Canada was efficient, I wouldn't exist: The miraculous success of Jonathan Ross Goodman", *Financial Post* (31 July 2017), online: <<https://financialpost.com/investing/goodman-rallies-from-near-death-bike-spill-for-drug-renaissance>>.

elsewhere, that specializes in bringing small market drugs to Canada, and indeed owes its very existence to miltefosine. As discussed earlier, there is no clear legal mechanism that could force Knight to bring miltefosine to market in Canada; meanwhile, no alternative producer wants to enter the Canadian market for a rarely used (albeit important) drug. Consequently, miltefosine can be accessed only through the Special Access Programme. Meanwhile in the United States, where it is marketed, it comes at a high price.¹⁴⁸¹ According to Sunyoto and colleagues, a full course of treatment in the US in 2018 was in the range of \$17,000USD and would be unlikely to be covered by insurance; for other conditions, like “treating free-living amoebas such as *Acanthamoeba keratitis*, miltefosine costs have reached US\$48,000”.¹⁴⁸² Ironically, before its commercial approval, the CDC had supplied access to miltefosine to treat these amoebic infections.¹⁴⁸³ The miltefosine experience casts further doubt on the suggestion that it was the failure to successfully obtain a PRV for artesunate, rather than the pursuit of profits, that led to similarly high pricing for that drug after its approval.¹⁴⁸⁴

Given the drug is obtained from Knight, similar cases in Canada have cost patients thousands of dollars when accessed through the SAP.¹⁴⁸⁵ Prices are high on the formal international market too; Knight’s price can be negotiated down, but only via bulk purchasing, something that has proven challenging for NGOs and for

¹⁴⁸¹ Cutaneous form of leishmaniasis is now likely endemic in the USA. See e.g., McIlwee, Bridget E, Stephen E Weis & Gregory A Hosler, “Incidence of Endemic Human Cutaneous Leishmaniasis in the United States” (2018) 154:9 JAMA Dermatol 1032, online:

<<http://archderm.jamanetwork.com/article.aspx?doi=10.1001/jamadermatol.2018.2133>>.

¹⁴⁸² Sunyoto, Temmy, Julien Potet & Marleen Boelaert, “Why miltefosine—a life-saving drug for leishmaniasis—is unavailable to people who need it the most” (2018) 3:3 BMJ Glob Health e000709, online: <<https://gh.bmj.com/lookup/doi/10.1136/bmjgh-2018-000709>>.

¹⁴⁸³ Centers for Disease Control and Prevention (CDC), “Investigational drug available directly from CDC for the treatment of infections with free-living amebae” (2013) 62:33 MMWR Morb Mortal Wkly Rep 666.

¹⁴⁸⁴ Frosch, Anne EP, Aileen Ahiskali & Chandy C John, “Unaffordable treatment for severe malaria highlights U.S. drug market pitfalls”, *STAT News* (11 June 2021), online: <<https://www.statnews.com/2021/06/11/unaffordable-treatment-for-severe-malaria-highlights-u-s-drug-market-pitfalls/>>.

¹⁴⁸⁵ O’Brien, Cillian, “Canadian blinded by water-borne parasite outraged by medication cost”, *CTV News* (17 July 2019), online: <<https://www.ctvnews.ca/health/canadian-blinded-by-water-borne-parasite-outraged-by-medication-cost-1.4512061>>.

smaller governments.¹⁴⁸⁶ Nonetheless, Knight remains the key global supplier. Even though the drug is off-patent, generics companies have stayed out of the larger global market as well; once again, public health successes may actually have worked against global access, because a decreasing number of cases as a result of successful elimination efforts in places like the Indian subcontinent may be deterring potential producers.¹⁴⁸⁷

In the US, the miltefosine episode inspired early calls for reform of the PRV, although these would not be heeded until the higher-profile issue of benznidazole (and its links to the headline-friendly Martin Shkreli).¹⁴⁸⁸ It nevertheless seems fairly clear that a company like Knight Therapeutics is far from the ideal global steward for an Essential Medicine for a Neglected Disease; a system that rewards such companies for bringing a pre-existing drug to a new market, without ensuring affordability in that market, let alone accessibility in high-burden LMICs, is a profoundly flawed one. As mentioned, the most obvious of these flaws is the fact that the PRV and similar mechanisms were never intended to target pre-existing drugs. Once again, this flaw is not necessarily a fatal one; if policymakers can overlook the issue of innovation, bringing an existing drug to market in a high-income country may also have societal benefits. However, in light of the actions of companies like Knight, the current system would have to be reformed in order to ensure those benefits are actually realized.

This was precisely the concern highlighted in 2017 by Ridley, the driver of the original PRV idea, who advocated reform on the grounds that “although the voucher program encourages drug development, the program does not ensure access to the drugs”, concluding “Congress should require that manufacturers have

¹⁴⁸⁶ Doshi, P, “US incentive scheme for neglected diseases: a good idea gone wrong?” (2014) 349:jul21 1 BMJ g4665–g4665, online: <<https://www.bmj.com/lookup/doi/10.1136/bmj.g4665>>.

¹⁴⁸⁷ Sunyoto, Temmy, Julien Potet & Marleen Boelaert, “Why miltefosine—a life-saving drug for leishmaniasis—is unavailable to people who need it the most” (2018) 3:3 BMJ Glob Health e000709, online: <<https://gh.bmj.com/lookup/doi/10.1136/bmjgh-2018-000709>>.

¹⁴⁸⁸ Reid, J et al., “Legislation governing the US incentive scheme for neglected diseases needs to be amended, urges MSF” (2014) 349:sep30 21 BMJ g5861–g5861, online: <<https://www.bmj.com/lookup/doi/10.1136/bmj.g5861>>.

a plan for ensuring drug access, especially for drugs for neglected diseases".¹⁴⁸⁹ Ridley had previously raised similar concerns while advocating for a PRV system to be introduced in the European Union, in the hopes that the EU would in the process avoid certain flaws of the US model.¹⁴⁹⁰ Ensuring that a drug is not only formally available but at an affordable price should be a clear prerequisite for reaping any financial reward. A related issue is that approval is also no guarantee the drug will remain on the market; this is another lesson that should have been learned from Orphan Drug legislation, where drugs like eflornithine and clofazimine vanished from the formal US market after being approved as Orphan Drugs, relegating access to other channels like the CDC Drug Service. As Ridley has highlighted, the award of the PRV should be contingent on a clear plan for affordable, sustainable access.¹⁴⁹¹ Making the award of the PRV itself contingent on a certain level of production for a minimum period at a reasonable cost would help avoid the issue of the absence of a freestanding legal obligation to continue manufacturing a drug.¹⁴⁹²

A more recent review by Ridley and colleagues again acknowledges the access issues associated with the PRV; however, while its focus on ensuring access in low-income, high-burden states is entirely logical in terms of the greatest public health benefit, it nevertheless overlooks the question of access in low-burden, high-income states.¹⁴⁹³ This is slightly ironic given how many drugs that received a PRV had been on the WHO MEML, and were available in at least some high-burden countries, years before the PRV was granted. In any case, there are some slightly different issues at play here for the country awarding the PRV, for low-

¹⁴⁸⁹ Ridley, David B, "Priorities for the Priority Review Voucher" (2017) 96:1 Am J Trop Med Hyg 14–15.

¹⁴⁹⁰ Ridley, David B & Alfonso Calles Sánchez, "Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases" (2010) 376:9744 Lancet 922–927.

¹⁴⁹¹ Ridley, David B, "Priorities for the Priority Review Voucher" (2017) 96:1 Am J Trop Med Hyg 14–15.

¹⁴⁹² Similar measures should be applied to the other two PRVs, both to improve access to those drugs and so as not to nudge pharma companies in those directions at the expense of Neglected Diseases.

¹⁴⁹³ Ridley, David B, Pranav Ganapathy & Hannah E Kettler, "US Tropical Disease Priority Review Vouchers: Lessons In Promoting Drug Development And Access: Article examines infectious disease drug and vaccine development." (2021) 40:8 Health Affairs 1243–1251, online: <<http://www.healthaffairs.org/doi/10.1377/hlthaff.2020.02273>>.

income/high-burden states, and for low-burden HICs other than the PRV-issuing state. In the first two cases, the use or transfer of the PRV is an obvious area for reform. First, in the PRV-awarding country, the PRV should not be redeemable until the drug is on shelves. While the manufacturer may incur costs accomplishing this before obtaining the value of the PRV, the value of the awarded-but-unredeemed PRV should in turn provide collateral for them to take the necessary steps, just as it has provided leverage for drugs like moxidectin to traverse the approval process in the first place. Similar strings should be tied to supplying high-burden territories. The innovation of drugs that are needed in high-burden jurisdictions of limited commercial interest is the *raison d'être* for the tropical disease PRV in the first place. As such, while the PRV-granting company cannot exert control over the regulatory bodies of other countries, a commitment to supply such countries for some minimum period of time should be considered. This may include a requirement to initiate the application process for regulatory approval in high-burden countries.

However, much like requiring a private company to produce a drug in perpetuity, it remains unrealistic to suggest that a company be required to take steps to enter every conceivable market as a condition of the PRV. This leaves low-burden countries like Canada in a situation much like they face now, though given past dependence on US supplies via the SAP, US market entry may yield some benefits for Canada in instances where approval is not accompanied by outrageous price hikes for existing drugs. The question thus arises whether Canada should initiate its own PRV equivalent to bring drugs to market. In truth, it is not clear that transposing the American PRV's particular balance of incentives will be effective. As Harris suggests, the incentive value to drug developers of a PRV is likely to be far less in Canada, because of its significantly smaller pharmaceutical market.¹⁴⁹⁴ Even where a company did obtain a Canadian PRV equivalent for a blockbuster drug, the financial return is going to be considerably lower than in the United

¹⁴⁹⁴ Harris, Emily, "Addressing the needs of Canadians with rare diseases: an evaluation of orphan drug incentives" (2018) 5:3 Journal of Law and the Biosciences 648–681, online: <<https://academic.oup.com/jlb/article/5/3/648/5088948>>.

States. As Harris puts it, “If companies cannot be bothered to market their product in Canada at all, it is reasonable to expect that a potential priority review of an NDS by Health Canada is going to be of very little value to a drug sponsor”.¹⁴⁹⁵ Certainly, a Canadian PRV aping the current American PRV is even less likely to stimulate a great degree of additional research into Neglected Diseases.

At the same time, different markets offer the possibility of adapting a PRV to local circumstances and local incentives. Ridley and Sanchez recognized this in the European Union, where it was suggested one potential perk could be to grant centralized review of the drug, rather than at the level of each member state.¹⁴⁹⁶ While this particular benefit is not directly applicable in Canada, an analogous perk beyond a PRV – one also particularly appropriate for Essential Medicines – would be to automatically include such drugs on a Canadian EML or national formulary or, in their absence, another list of important drugs, making them eligible for federal reimbursement. By targeting important but absent drugs like Essential Medicines (particularly those used in small quantities), this could be done with relatively little financial burden on the state, while promoting equitable access for all Canadians, including the marginalized communities disproportionately affected by access barriers.

Furthermore, by targeting existing drugs that already form the standard of care, Canada could learn from the PRV experience and avoid the inevitable disappointment of failure to accelerate truly novel research, while nevertheless bringing a useful product to the formal market. To this end, rather than imposing requirements for new trials on old drugs, as in the post-benznidazole reforms to the US Tropical Disease PRV, Canada could instead be more open to accepting existing evidence for Essential Medicines that already constitute the standard of care. Still, before going too far down this road, it is worth recalling the sensible caution by Harris that a PRV for the Canadian market might simply not be as

¹⁴⁹⁵ Harris, Emily, “Addressing the needs of Canadians with rare diseases: an evaluation of orphan drug incentives” (2018) 5:3 *Journal of Law and the Biosciences* 648–681, online: <<https://academic.oup.com/jlb/article/5/3/648/5088948>>.

¹⁴⁹⁶ Ridley, David B & Alfonso Calles Sánchez, “Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases” (2010) 376:9744 *The Lancet* 922–927, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673610606691>>.

appealing.¹⁴⁹⁷ At the very least, other tweaks will likely be required. For instance, it would be necessary to determine Canada's bureaucratic and logistical capacity for even accommodating such a program in the first place; these logistical matters are beyond the scope of this thesis but would merit serious consideration. After all, given the expected returns to commercial participants, a seven-figure administrative fee like that in the USA would be less feasible as a means of supporting an enlarged bureaucracy. Still, the broader concept of tying the fate of existing Essential Medicines of limited commercial appeal to incentives around more lucrative medicines is at least worth examining.

In closing this section, it is also worth reflecting once more upon the fact that, despite the stereotype contrasting Canadian socialized medicine with the free market free-for-all of American healthcare, the US has in many respects been more interventionist when it comes to medicines for Neglected Diseases. The US Government has passed laws, from the *Orphan Drug Act* to the regulations establishing the tropical disease PRV, to explicitly encourage the development and marketing of commercially unappealing drugs for Neglected Diseases. Where such drugs exist but are not formally marketed, the government, via the CDC Drug Service, still plays a central role in obtaining and distributing a range of them, free of charge. This is a reminder that even in the land of the free, the free market is not sufficient to ensure access to Essential Medicines for Neglected Diseases. Even if it does not adapt any of America's more specific approaches, Canada should learn this broader lesson.

¹⁴⁹⁷ Harris, Emily, "Addressing the needs of Canadians with rare diseases: an evaluation of orphan drug incentives" (2018) 5:3 *Journal of Law and the Biosciences* 648–681, online: <<https://academic.oup.com/jlb/article/5/3/648/5088948>>.

Chapter 14: Other roles for the State

Federal procurement

As such, there are other areas where the federal government could play a valuable role in improving access to off-patent Essential Medicines for Neglected Diseases. One would be an expanded role for federal procurement for these drugs. Such a procurement strategy could be applied both to approved and unapproved drugs, with relatively minor tweaks. A limited scope of procurement – rooted in ensuring access to the recognized standard of care – would focus on important medicines poorly served by the commercial market. This could include both currently unmarketed drugs and important drugs that are currently on the market but prone to shortages or at risk of discontinuation. It would serve small, disproportionately marginalized communities, and serve as a complement to current efforts around high-priced drugs for Rare Diseases. The process of developing a Canadian EML – with reference to the WHO MEML and Canadian treatment guidelines – could, and should, in turn inform which drugs should be federally procured.

It is important to note that this would simply be an extension of existing practice rather than a novel activity. The government has long procured drugs and operated a range of stockpiles, such as for EUNDS. Of late, its role in procurement has been exemplified by COVID-19 vaccines, and its maintenance of the Central Vaccine Inventory alongside its distribution to provinces.¹⁴⁹⁸ This role is further illustrated by the aforementioned COVID-19 Critical Drug Reserve, which held multiple off-patent Essential Medicines.¹⁴⁹⁹ In fact, the idea of a federal stockpile specific to unapproved Essential Medicines for Neglected Diseases is itself hardly new; nor is the idea that such a stockpile would simplify physician access by removing the barrier of needing to deal with both Health Canada and the drug company for a single access request. Canada once maintained a stockpile of drugs

¹⁴⁹⁸ See e.g., Dubois, Stephanie, “Canada’s vaccine reserve exceeds 4 million doses, prompting calls for better tracking of donations”, *CBC News* (17 December 2021), online: <<https://www.cbc.ca/news/health/extra-vaccines-donation-pledge-1.6288998>>.

¹⁴⁹⁹ Health Canada, “Government of Canada establishes Critical Drug Reserve to bolster Canada’s supply of drugs used to treat COVID-19”, (14 April 2021), online: <<https://www.canada.ca/en/health-canada/news/2021/04/government-of-canada-establishes-critical-drug-reserve-to-bolster-canadas-supply-of-drugs-used-to-treat-covid-19.html>>.

bearing a close resemblance to the CDC Drug Service Formulary. According to an account from the mid-1980s:

A few "emergency drugs" that are particularly difficult to obtain (e.g., from overseas suppliers) or that are rarely or urgently required are exceptions to the usual method of supply and are normally available without charge from the bureau's stocks at the National Defence Medical Centre, in Ottawa. Such antiparasitic drugs include injectable chloroquine, quinine, melarsoprol, sodium stibogluconate and suramin, as well as bithionol, diloxanide furoate and nifurtimox, all three for oral use.¹⁵⁰⁰

The precise details surrounding the demise of this stockpile are unclear, but the National Defence Medical Centre was itself shuttered in the 1990s. The consequence, however, is that over three decades later, nearly all of these drugs – all for Neglected Diseases, and all but bithionol found on the WHO MEML – are now only available from the manufacturer via the SAP rather than directly from the government. As such, Canada has actually regressed in some respects when it comes to accessing Essential Medicines for Neglected Diseases.

It should be noted that stockpiles of unmarketed Essential Medicines for Neglected Diseases can also exist at the provincial level, as seen earlier with the example of diphtheria antitoxin.¹⁵⁰¹ However, given that such provincial stockpiles are dependent upon federal measures to permit unmarketed drugs into the country, the focus of this section will remain federal. The most famous federal stockpile is the National Emergency Stockpile System (NESS). Today managed by PHAC, the NESS has two depots in Ottawa, a further nine warehouses across the

¹⁵⁰⁰ White, G F & MJ Davis, "Antiparasitic drugs: availability and regulatory requirements for 'emergency' supply" (1985) 132:3 Can Med Assoc J 273–274.

¹⁵⁰¹ As discussed earlier, see e.g., See e.g., Alberta Health Services, *Alberta Public Health Disease Management Guidelines Diphtheria* (Government of Alberta, 2019), online <<https://open.alberta.ca/publications/diphtheria>>; Ontario Ministry of Health and Long-Term Care, *Diphtheria Guide for Health Care Professionals* (Government of Ontario, 2018), online: <http://www.health.gov.on.ca/en/pro/publications/disease/docs/Diphtheria_Guide_042018.pdf>.

country, and a large number of pre-positioned sites all over Canada.¹⁵⁰² Originally created in the 1950s in response to the threat of nuclear war, its ambit was expanded to other disasters, and to peacetime as well as wartime, in the 1960s.¹⁵⁰³ Following the 9/11 terrorist attacks in 2001, and the Severe Acute Respiratory Syndrome (SARS) epidemic in 2004, the NESS expanded its stock of pharmaceuticals to respond to pandemics (e.g., antivirals for pandemic flu) and biological warfare (e.g., anthrax antitoxin).¹⁵⁰⁴

Of course, when suggesting a larger role for federal procurement and stockpiling, it must be acknowledged that the management of the NESS has come under heavy criticism. This has occurred most recently during the COVID-19 pandemic.¹⁵⁰⁵ Such criticism is also not a new phenomenon unique to the COVID-19 response, however; stockpiling of unmarketed drugs has been the target of past criticism as well. For example, in the Auditor General of Canada's 2005 review of Canada's emergency preparedness, the specific example of the NESS using the SAP to provide medical countermeasures to frontline responders was emphasized when reaching the conclusion that the SAP was inappropriate for such purposes, and that a better legal structure for accessing such drugs needed to be established.¹⁵⁰⁶ As will be recalled, this ultimately led to the establishment of the EUNDS approval pathway.

¹⁵⁰² Public Health Agency of Canada, "Evaluation of the National Emergency Stockpile System (NESS)" (April 2011), online: <<https://www.canada.ca/en/public-health/corporate/mandate/about-agency/office-evaluation/evaluation-reports/evaluation-national-emergency-stockpile-system.html#toc>>.

¹⁵⁰³ Public Health Agency of Canada, "Evaluation of the National Emergency Stockpile System (NESS)" (April 2011), online: <<https://www.canada.ca/en/public-health/corporate/mandate/about-agency/office-evaluation/evaluation-reports/evaluation-national-emergency-stockpile-system.html#toc>>.

¹⁵⁰⁴ Public Health Agency of Canada, "Evaluation of the National Emergency Stockpile System (NESS)" (April 2011), online: <<https://www.canada.ca/en/public-health/corporate/mandate/about-agency/office-evaluation/evaluation-reports/evaluation-national-emergency-stockpile-system.html#toc>>.

¹⁵⁰⁵ See e.g., Leo, Geoff, "Health minister reviewing management of Canada's emergency stockpile", *CBC News* (15 April 2020), online: <<https://www.cbc.ca/news/canada/saskatchewan/health-minister-emergency-stockpile-1.5530081>>; Laing, Scott & Ellen Westervelt, "Canada's National Emergency Stockpile System: time for a new long-term strategy" (2020) 192:28 CMAJ E810-E811, online: <<http://www.cmaaj.ca/lookup/doi/10.1503/cmaj.200946>>.

¹⁵⁰⁶ Office of the Auditor General, "National security in Canada: the 2001 Anti-Terrorism Initiative : air transportation security, marine security, and emergency preparedness." (2005) 2005 Report of the Auditor General of Canada at p.26.

Not all such drugs have been approved via the EUNDS pathway in the interim, however. As part of the push for regulatory reform that ultimately yielded the recent reforms to the SAP, a further component was proposed focusing on stockpiling unmarketed drugs for health emergencies.¹⁵⁰⁷ Although this component did not move forward with the rest of the SAP reforms, the proposal for a “Public or Canadian Armed Forces Health Emergencies - Drugs for Immediate Use or Stockpiling” access framework offers further guidance on how a larger stockpile might work for unmarketed drugs.¹⁵⁰⁸ In terms of the proposed mechanism itself, it would be akin to the UPHN, only with the option of stockpiling alongside immediate use, enabling a public health official “to request that a manufacturer sell them a quantity of drug that is not authorized for sale in Canada in order to respond to, or prepare for a public or military health event, incident or emergency”.¹⁵⁰⁹ However, unlike the UPHN, this proposal did not even require the drug to be approved by a foreign regulatory authority.¹⁵¹⁰ All of this goes to show that there is nothing barring the federal government from playing a direct role in purchasing the necessary tools (whether or not they have domestic market approval), stockpiling them to ensure they are on hand, and distributing them when they are needed. As noted above, Canada may already be moving in the direction of making wider use of stockpiling as a dynamic tool at the federal level, as exemplified by the recently established (albeit temporary) Critical Drug Reserve

¹⁵⁰⁷ “Regulations Amending Certain Regulations Concerning the Sale of Drugs (Public or Canadian Armed Forces Health Emergencies)” Canada Gazette, Part I, (11 May 2019) Volume 153, Number 19, online: <<https://gazette.gc.ca/rp-pr/p1/2019/2019-05-11/html/reg1-eng.html>>.

¹⁵⁰⁸ “Regulations Amending Certain Regulations Concerning the Sale of Drugs (Public or Canadian Armed Forces Health Emergencies)” Canada Gazette, Part I, (11 May 2019) Volume 153, Number 19, online: <<https://gazette.gc.ca/rp-pr/p1/2019/2019-05-11/html/reg1-eng.html>>.

¹⁵⁰⁹ Health Canada, “Draft Guidance Document: Public or Canadian Armed Forces Health Emergencies - Drugs for Immediate Use or Stockpiling” (10 May 2019), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/public-involvement-consultations/drug-products/notice-draft-guidance-drugs-immediate-use-stockpiling-public-canadian-armed-forces/draft-guidance-drugs-immediate-use-stockpiling-eng.pdf>> at p.6.

¹⁵¹⁰ Health Canada, “Draft Guidance Document: Public or Canadian Armed Forces Health Emergencies - Drugs for Immediate Use or Stockpiling” (10 May 2019), online: <<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/public-involvement-consultations/drug-products/notice-draft-guidance-drugs-immediate-use-stockpiling-public-canadian-armed-forces/draft-guidance-drugs-immediate-use-stockpiling-eng.pdf>> at p.10.

for COVID-19 drugs, which included multiple off-patent medicines found on the WHO MEML.¹⁵¹¹

Having the federal government operate as the initial purchaser and subsequent distributor of a selection of important drugs would serve a number of other purposes as well, even before considering how it might set the stage for formal approval of those absent from the market.¹⁵¹² First, a centralized purchase by the federal government would mean the government itself would have control over the available supply. This would give it greater ability to take measures to confirm the quality of drugs received before distribution, thus allowing it to meet a key regulatory goal in a different way. Central procurement would also reduce uncertainty about the availability of the drug. The consequences would be particularly important for unapproved drugs, as the government would not only be able to grant a SAP authorization but also fill that authorization directly from its stockpile, rather than requiring an applicant to take the separate step of approaching the manufacturer. In turn, acting as sole purchaser places the government in a better position to take other actions to guard against shortages, whether a drug is unapproved, or approved but prone to shortages. As purchaser and distributor, information about supply and demand becomes first-hand information for the government, enabling a faster, more effective response when supply issues arise. Even where expectations of federal performance are tempered based on past experience with federal stockpiles, the government should still be better equipped than any individual applicant to the SAP to tackle major disruptions, such as a shortage from one supplier or a massive price hike from another, and respond by seeking out new supplies or negotiating new prices. Acting as the sole purchaser would also provide leeway for the government to negotiate with the manufacturer over other conditions of supply. Given the government

¹⁵¹¹ Health Canada, “Government of Canada establishes Critical Drug Reserve to bolster Canada’s supply of drugs used to treat COVID-19”, (14 April 2021), online: <https://www.canada.ca/en/health-canada/news/2021/04/government-of-canada-establishes-critical-drug-reserve-to-bolster-canadas-supply-of-drugs-used-to-treat-covid-19.html>.

¹⁵¹² To be clear, the precise manner of distribution is dependent on numerous factors and is beyond the scope of this thesis. It could include distribution to provincial stockpiles (as with DAT), institutional stockpiles (as with parenteral artesunate), or direct distribution upon request (like the CDC Drug Service formulary).

already does this to a limited degree, and that it has not resulted in greater government liability in practice, the benefits to the health of Canadians would seem to outweigh the hypothetical risks of greater government involvement with unapproved drugs; however, this in turn could also be addressed via formal approval.

Another benefit is that a single purchaser contracting for a fixed amount of a drug for the entire country could help provide the market with the stability necessary for sustainable access to at least some of the drugs whose market status is precarious, or that are not currently available at all. For instance, it could guarantee a certain minimum purchase, which would be tied to the expected access needs across the country, plus some extra to accommodate unforeseen circumstances. A guaranteed market would be an incentive for market entry, or for sustaining production of a marginal drug. Such an approach would also help to maintain price stability, with the price being fixed (or otherwise arranged) via contract. As such, it would complement a streamlined approval pathway for medically important but commercially negligible drugs.

Federal control over these drugs also addresses the coverage issue; federally purchased Essential Medicines could be made uniformly available across Canada, outside the scope of provincial formularies, and as part of (or in addition to) future federal lists like a Canadian EML and national formulary. Particularly if the costs are covered by the federal government, provinces are unlikely to refuse, while the unmet needs of disproportionately vulnerable groups will be better met in the bargain. Restricting this approach to a small number of drugs defined with reference to tools like the WHO MEML, Canadian EML, and treatment guidelines will help control costs; while predicting a precise dollar figure is beyond the scope of this thesis, unless procurement is tendered to Martin Shkreli, it seems distinctly unlikely the final price tag will come to the annual half billion dollars previously earmarked by the government to serve similarly small populations of Canadians requiring high-priced drugs for Rare Diseases.

Here there is another lesson to be drawn from Canada's existing stockpiles. This lesson involves the amount of money Canada is already willing to spend on

ensuring access to both approved and unapproved tools to combat the rarest of infectious diseases via the NESS. Even as Essential Medicines for other diseases more regularly encountered languish, Canada currently expends considerable resources ensuring access to tools to tackle an infectious disease that is not merely uncommon in Canada, but nonexistent: smallpox. Smallpox was rendered non-endemic in Canada by 1946, with no confirmed cases in Canada since 1962, and the global eradication of the disease declared in 1980.¹⁵¹³ Smallpox vaccination has long been dropped as a widespread preventative measure in this country; regular vaccination ceased in Canada in 1972, meaning smallpox vaccine has lingered for half a century primarily in relation to fears of biological warfare.¹⁵¹⁴ At the international level, smallpox vaccine was removed from the WHO MEML in 1982. In the interim, however, Canada has continued to purchase smallpox vaccine, both in formulations with market approval and formulations without.¹⁵¹⁵ The latter have been purchased by the Government of Canada via the SAP. In 2013, over five decades after the last confirmed case in Canada, a formulation of smallpox vaccine previously obtained via the SAP received Health Canada approval via the EUNDS pathway.¹⁵¹⁶ In March of 2021, the Canadian government placed a new order worth over \$30 million USD for that version of the smallpox vaccine from its Danish manufacturer.¹⁵¹⁷ That same year, Health Canada also approved tecovirimat (TPOXX), the first oral treatment for smallpox, via the EUNDS pathway, forty years after the disease had been eradicated.¹⁵¹⁸ This approval had been preceded by a

¹⁵¹³ McIntyre, J W & C S Houston, "Smallpox and its control in Canada" (1999) 161:12 CMAJ 1543–1547.

¹⁵¹⁴ Nicolle, Lindsay, "Smallpox 2003" (2003) 14:5 Can J Infect Dis 247–248.

¹⁵¹⁵ Public Health Agency of Canada, *Canadian immunization guide*. (2014) at p.126.

¹⁵¹⁶ See e.g., Bavarian Nordic A/S, "Health Canada Extends Approval of IMVAMUNE to Immunization against Monkeypox and Orthopox Viruses", (12 November 2020), online: <<https://www.globenewswire.com/news-release/2020/11/12/2125193/0/en/Health-Canada-Extends-Approval-of-IMVAMUNE-to-Immunization-against-Monkeypox-and-Orthopox-Viruses.html>>.

¹⁵¹⁷ "Bavarian Nordic Receives Additional Smallpox Vaccine Order from the Canadian Government" (22 March 2021), online: <<https://www.globenewswire.com/news-release/2021/03/22/2196559/0/en/Bavarian-Nordic-Receives-Additional-Smallpox-Vaccine-Order-from-the-Canadian-Government.html>>.

¹⁵¹⁸ SIGA Technologies Inc, "SIGA Announces Health Canada Regulatory Approval of Oral TPOXX®" (1 December 2021), online: <<https://www.globenewswire.com/news->

PHAC contract to purchase \$33 million worth of the drug.¹⁵¹⁹ With that sort of money on the table, it is not surprising that this producer entered the Canadian market. In the US, both vaccine and drug had received PRVs via the Material Threat Medical Countermeasure stream.¹⁵²⁰ Canada in turn simply offered a promising business proposition. While keeping the broader federal budget sustainable means paying reasonable prices – not those dictated by Martin Shkreli – for old drugs, Canada’s ability to invest considerable resources to ensure access to a no-longer Essential Medicine for the hypothetical threat of a disease not seen in Canada since the 1960s demonstrates that it should be able to do the same for diseases that tangibly affect tens or even hundreds of Canadians annually.¹⁵²¹

Ironically enough, the events of 2022 have demonstrated that this was a sound investment, and not because of bioterrorism, but because of the spread of a disease previously found only in LMICs to Canada. This disease is monkeypox, an orthopox virus related to smallpox and endemic to parts of Africa. Its unprecedented spread in 2022, including over a thousand cases in Canada as of this writing, have demonstrated the value of Canada being one of very few countries with a stockpile of a vaccine approved not only for smallpox but also monkeypox.¹⁵²² At the same time, both the Bavarian Nordic vaccine and tecovirimat (being used off-label for monkeypox) were approved as EUNDS, rather than undergoing human trials; as such, their utility remains untested in practice. By

[release/2021/12/01/2344305/9738/en/SIGA-Announces-Health-Canada-Regulatory-Approval-of-Oral-TPOXX.html](https://www.globeandmail.com/health/health-news/article/siga-announces-health-canada-regulatory-approval-of-oral-tpoxx.html)>.

¹⁵¹⁹ SIGA Technologies Inc, “SIGA Announces Public Health Agency of Canada Contract Award to Purchase Up To Approximately \$33 Million of Oral TPOXX®” (13 January 2021), online: <<https://www.globenewswire.com/news-release/2021/01/13/2158282/9738/en/SIGA-Announces-Public-Health-Agency-of-Canada-Contract-Award-to-Purchase-Up-To-Approximately-33-Million-of-Oral-TPOXX.html>>.

¹⁵²⁰ Ridley, David B. Priority Review Vouchers (Website). Durham (NC): Duke University Fuqua School of Business, online: <<https://sites.fuqua.duke.edu/priorityreviewvoucher>>. Accessed May 1, 2022.

¹⁵²¹ Smallpox vaccine was present on the inaugural WHO MEML in 1977 and removed in 1982 after the disease was eradicated.

¹⁵²² Bavarian Nordic A/S, “Health Canada Extends Approval of IMVAMUNE to Immunization against Monkeypox and Orthopox Viruses”, (12 November 2020), online: <<https://www.globenewswire.com/news-release/2020/11/12/2125193/0/en/Health-Canada-Extends-Approval-of-IMVAMUNE-to-Immunization-against-Monkeypox-and-Orthopox-Viruses.html>>.

contrast, longstanding Essential Medicines are already well understood; a similar investment to address Neglected Diseases would similarly pay dividends.

Foreign regulatory authorities and the *International Pharmacopoeia*

A shared theme across recent changes in how unmarketed medicines are accessed in Canada is that they have almost all pointed the way towards expanded acceptance of approval by foreign regulatory authorities. Mechanisms like the UPHN, the reformed SAP, and the interim orders for drugs used in the response to COVID-19 discussed earlier have all explicitly incorporated approval by certain other jurisdictions, particularly the US FDA and the European Medicines Agency.¹⁵²³ These measures have encompassed drugs completely absent from the Canadian market, as well as alternate suppliers and different formulations of approved drugs. Other recent changes to the *Food and Drug Regulations*, such as in circumstances where “Her Majesty in right of Canada has entered into a contract for the procurement of the designated COVID-19 drug”, have cast the net even wider.¹⁵²⁴ In that instance, pre-positioning of COVID-19 drugs without an NOC is permitted even for drugs for which only “an application has been submitted to a foreign regulatory authority to authorize the sale of the designated COVID-19 drug”.¹⁵²⁵ In other words, the drug does not even have to be approved by any foreign regulatory authority at this stage, let alone particular jurisdictions such as the US or the EU. When all these changes are considered together, the overarching signal is that foreign standards, or at least a subset of trusted ones, should be embraced in taking the next step: formal approval, at least for otherwise unavailable standard of care drugs.

In recent decades Canada has been reluctant to permit foreign reviews to be used in place of its own. Unfortunately, as the preceding pages have illustrated, sometimes this domestic review never occurs. To the extent this approach inhibits access to standard-of-care Essential Medicines, it no longer seems the best way of

¹⁵²³ And, in the case of UPHN, Switzerland’s Swissmedic.

¹⁵²⁴ C.08.009.02, *Food and Drug Regulations*. See “Regulations Amending the Food and Drug Regulations (Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19): SOR/2021-45”, *Canada Gazette, Part II*, Vol.155, No.7 (31 March 2021).

¹⁵²⁵ *Food and Drug Regulations* C.08.009.03 (1)(a)(i)(B).

ensuring safe, effective, good quality drugs are made formally available in Canada (if indeed it ever was). As touched upon earlier, Canada has also been reliant on inspections and similar regulatory activities by foreign bodies such as the US FDA, especially where drugs are manufactured overseas.¹⁵²⁶ While issues of enforcement are beyond the scope of this thesis, Canadian standards cannot credibly be used as an excuse to restrict acceptance of unapproved drugs if those same standards are also not being met, and enforced, for approved drugs. Pragmatism has to begin somewhere. And if Canada is to move towards accepting foreign drug reviews for formal availability, Essential Medicines seem a good place to start. After all, these are drugs whose global importance is established, and whose safety and efficacy is already understood. Furthermore, rather than taking Canada into uncharted territory, such an approach would actually reflect Canada's lengthy history of drawing upon foreign reference standards for pharmaceuticals.

The longstanding incorporation of foreign standards directly into the *Food and Drugs Act* illustrates Canada's historical approach of not only drawing upon foreign and international reference standards for pharmaceuticals, but doing so in place of developing its own. As noted early in this thesis, the first explicit standards adopted for pharmaceuticals in Canada, under the 1884 *Adulteration Act*, were set by reference to foreign pharmacopoeias.¹⁵²⁷ In the absence of its own standards, Canada made the British Pharmacopoeia its default reference unless another foreign reference was explicitly used.¹⁵²⁸ Recognition of foreign reference standards would continue to impact other laws for years, with further international implications; as but one example, Canada's 1939 trade agreement with the United States places tariffs on medicines, but exempts from these tariffs those drugs found

¹⁵²⁶ One particularly egregious investigation found Health Canada far behind the US FDA not merely in inspection of foreign drug manufacturing facilities, but manufacturing facilities in Canada; this was compounded by lack of transparency. See e.g., Bruser, David & Jesse McLean, "Canadians kept in dark about defective drugs", *The Toronto Star* (11 September 2014), online: <https://www.thestar.com/news/canada/2014/09/11/canadians_kept_in_dark_about_defective_drugs.html>.

¹⁵²⁷ Art. 2(a)(1), *An Act To Amend and To Consolidate as Amended the Several Acts Respecting the Adulteration of Food and Drugs* 1884 C. 34 S. C.

¹⁵²⁸ Allmark, MG, "The Pharmacopoeias and Their Status Under the New Canadian Food and Drugs Act" (1954) 9:5 *Food, Drug, Cosmetic Law Journal* 251–255.

in specific reference standards.¹⁵²⁹ Even after Canada ceased to rely solely on foreign standards, it has continued to explicitly recognize select national and international standards as reference standards under the *Food and Drugs Act*.¹⁵³⁰

In fact, Canada has long set the groundwork for accepting international standards not merely for pharmaceuticals in general, but for Essential Medicines for Neglected Diseases in particular. The *International Pharmacopoeia*, sometimes referred to by its Latin name the *Pharmacopoeia Internationalis*, is, like the EML, a list of medicines developed under the auspices of the World Health Organization. In and of itself, the *International Pharmacopoeia* occupies a grey area in terms of its legal status; as discussed earlier, the WHO's intention to pass legally binding regulations ultimately fizzled in the early 1950s. Nonetheless, the *International Pharmacopoeia* exerts legal influence in multiple contexts. Per the introduction to the most recent edition, released in 2019:

The International Pharmacopoeia (Ph.Int.) comprises a collection of recommended procedures for analysis and specifications for the determination of “pharmaceutical substances” (active pharmaceutical ingredients), excipients and “dosage forms” (general texts and individual finished pharmaceutical products) that is intended to serve as source material for reference or adaptation by any World Health Organization (WHO) Member State wishing to establish pharmaceutical requirements. *The pharmacopoeia, or any part of it, shall have legal status whenever a national or regional authority expressly introduces it into appropriate legislation* [emphasis added].¹⁵³¹

¹⁵²⁹ In this case the British or United States Pharmacopoeia, the Canadian Formulary and the French Codex. *Canada-U.S. Trade Agreement* (1939), Schedule I.

¹⁵³⁰ Food and Drugs Act (R.S.C., 1985, c. F-27), Schedule B.

¹⁵³¹ World Health Organization, *International Pharmacopoeia*, 9th ed. (2019), online: <<https://apps.who.int/phint/2019/index.html#d/b.1>>.

In turn, Canada is among the countries that has taken this step of expressly introducing the *International Pharmacopoeia* into its *Food and Drugs Act* as one of its reference standards. Schedule B incorporates the “most recent editions, including all errata, supplements, revisions and addenda” of a list of eight national and international references, including the *International Pharmacopoeia*.¹⁵³² Indeed, Canada recognized the utility of the *International Pharmacopoeia* even before it was finalized. In 1950, while the inaugural version of the long-gestating tool was still being developed, Morrell, the director of Health and Welfare Canada’s Food and Drugs division highlighted Canada’s participation in its development, as well as the value of relying on shared standards.¹⁵³³ He emphasized that unless there were important reasons for doing so, adapting a special Canadian standard rather than a shared one was to be avoided; there is, after all “no point in having differences just to be different” when it comes to pharmaceutical regulation.¹⁵³⁴ In 1954, Canada revised the *Food and Drugs Act* to incorporate the nascent *International Pharmacopoeia* as one of the reference standards within the *Act*, where it has remained ever since. Responding to the 1954 amendments, Allmark, another official with Health and Welfare Canada, stated that “Canada, unlike a good many other countries, has never considered that it was necessary to establish a pharmacopoeia of her own”.¹⁵³⁵ “And now,” he added, “since the publication of the international pharmacopoeia by the World Health Organization, the publication of which received the support of the Canadian representatives to the World Health Organization, the possibility of establishing a Canadian pharmacopoeia seems even

¹⁵³² In addition to the *International Pharmacopoeia*, the others are: *European Pharmacopoeia* (Ph.Eur.); *Pharmacopée française* (Ph.F.); *British Pharmacopoeia* (B.P.); *the Pharmaceutical Codex: Principles and Practices of Pharmaceuticals* [British]; *The Canadian Formulary* (C.F.); *The National Formulary* (N.F.) [American]; and *the United States Pharmacopoeia*.
Schedule B, *Food and Drugs Act* (R.S.C., 1985, c. F-27).

¹⁵³³ Morrell, CA, “Administration of the Canadian Food and Drugs Act” (1950) 5:8 Food Drug Cosm LJ 656.

¹⁵³⁴ Morrell, CA, “Administration of the Canadian Food and Drugs Act” (1950) 5:8 Food Drug Cosm LJ 656.

¹⁵³⁵ Allmark, MG, “The Pharmacopoeias and Their Status Under the New Canadian Food and Drugs Act” (1954) 9:5 Food, Drug, Cosmetic Law Journal 251–255.

more remote”.¹⁵³⁶ Today, Schedule B of the *Food and Drugs Act* looks a lot like it did in 1954.¹⁵³⁷ And while pharmaceutical science has evolved in the interim, Canada has in fact never established its own comprehensive pharmacopoeia, just as it has yet to develop a national formulary or EML. Of the foreign and international standards that Canada recognizes, it is the *International Pharmacopoeia* that is most important for Neglected Diseases.

Canadian recognition of the *International Pharmacopoeia* has particular implications for Essential Medicines more broadly, as the two have become intimately linked since the late 1970s.¹⁵³⁸ Today’s *International Pharmacopoeia* quite intentionally “specifies primarily the quality of essential medicines” found on the WHO MEML and the WHO MEML for Children.¹⁵³⁹ As such, virtually all the key Essential Medicines highlighted in this paper – including albendazole, nifurtimox, artemisinin, benznidazole, cycloserine, ivermectin, melarsoprol, and pyrimethamine – appear in the *International Pharmacopoeia*. This is especially noteworthy given that some or all of these Essential Medicines for Neglected Diseases are absent from the other references incorporated into Schedule B, all of which are based in HICs.

There are further practical implications. The *International Pharmacopoeia* further ties the WHO MEML to “other United Nations (UN)/WHO documents

¹⁵³⁶ Allmark, MG, “The Pharmacopoeias and Their Status Under the New Canadian Food and Drugs Act” (1954) 9:5 Food, Drug, Cosmetic Law Journal 251–255.

¹⁵³⁷ What then to make of the *Canadian Formulary*, which remains on Schedule B of the *Food and Drugs Act* to this day? This *Canadian Formulary* is not a stand-alone reference but a mere supplement to the *British Pharmacopoeia*. It was created in the 1930s, after it was determined during the revision of the *British Pharmacopoeia* that local governments “in any part of the Empire” should be able to introduce “Supplements or Addenda” in order to “meet any local requirements or introduce any modifications or alternatives desired”. For more on the Canadian Formulary and the reasoning behind it, see Henderson, V E & G H Lucas, “The Canadian Formulary and Reference Companion” (1933) 28:5 Can Med Assoc J 497–498; Allmark, MG, “The Pharmacopoeias and Their Status Under the New Canadian Food and Drugs Act” (1954) 9:5 Food, Drug, Cosmetic Law Journal 251–255. It is worth observing, however, that this model of adopting international standards while adapting them for local needs is also the model of the WHO MEML.

¹⁵³⁸ See e.g., Kopp, Sabine & Lembit Rago. “The International Pharmacopoeia in the changing environment” (2007) 9:3–4 Pharmaceuticals, Policy and Law 357–368. This process began with the initial 1975 report on Essential Medicines, and came to fruition by the time of the second edition of the WHO MEML in 1979.

¹⁵³⁹ World Health Organization, *International Pharmacopoeia*, 9th ed. (2019), online: <<https://apps.who.int/phint/2019/index.html#d/b.1>>.

recommending the use of medicines for the treatment of specific diseases and/or for use by treatment programmes”.¹⁵⁴⁰ As such, normative guidance at the international level further informs both the WHO MEML and the *International Pharmacopoeia*, just as it could inform the process of developing a Canadian EML and the accompanying review of Essential Medicines. More recently, the *International Pharmacopoeia* has also become explicitly linked to regulatory standards for drug quality via WHO Prequalification, a standard intended to be equivalent to the standards of a Stringent Regulatory Authority like Canada.¹⁵⁴¹ Given that Canada explicitly recognizes the *International Pharmacopoeia*, it should by extension already recognize the standards that underpin WHO Prequalification of Essential Medicines, a step towards recognition of international standards for pharmaceuticals that disproportionately impact Neglected Diseases.

WHO Prequalification

In essence, WHO Prequalification is intended to establish a high standard for quality considered equivalent to that of the parallel concept of a Stringent Regulatory Authority, which is a national regulatory authority with exacting standards.¹⁵⁴² Today many international programmes, both within the UN and those run by NGOs and similar organizations, will accept a drug approved by WHO Prequalification or by an SRA.¹⁵⁴³ With the emergence of WHO Prequalification, international standards for quality assurance are becoming intimately woven into

¹⁵⁴⁰ World Health Organization, *International Pharmacopoeia*, 9th ed. (2019), online: <<https://apps.who.int/phint/2019/index.html#d/b.1>>.

¹⁵⁴¹ World Health Organization, *International Pharmacopoeia*, 9th ed. (2019), online: <<https://apps.who.int/phint/2019/index.html#d/b.1>>.

¹⁵⁴² Currently, the WHO list of SRA's includes Canada, Australia, Japan, the United Kingdom, the United States, all four European Free Trade Association (EFTA) states, and all 27 European Union (EU) states. An SRA is a regulatory authority which is a member or an observer of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), or is associated with an ICH member through a legally binding mutual recognition agreement. It should be noted this is an informal version of the definition, which is itself still technically an interim one. Indeed, the technical interim definition still refers to Canada as an observer to the ICH, as it was at the time, although it has since become a member. WHO Expert Committee on Specifications for Pharmaceutical Preparations & World Health Organization, eds, WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report, WHO technical report series 1003 (Geneva, 2017) at p.34.

¹⁵⁴³ As an example, see Médecins Sans Frontières, “MSF Medical Product Qualification Scheme” (October 2016), online: <<https://www.msf.org/msf-medical-product-qualification-scheme>>.

the fabric of access to Essential Medicines with an emphasis on those for Neglected Diseases. In the process, they are tying together the WHO MEML, the *International Pharmacopoeia*, international treatment guidelines, and other programming by international agencies, national governments, and NGOs alike.

WHO Prequalification is not itself a novel concept; the WHO first established a prequalification programme for vaccines in 1987.¹⁵⁴⁴ Those standards were initially conceived to assist UNICEF in its vaccination programmes.¹⁵⁴⁵ The idea caught on; in 1992, the World Health Assembly passed a resolution that all vaccines used in national immunization programmes should meet these WHO requirements.¹⁵⁴⁶ Meanwhile, the wide divergence between UN agencies in their quality requirements for other pharmaceuticals had been a longstanding issue, impacting areas like procurement.¹⁵⁴⁷ As such, the idea of initiating WHO Prequalification for drugs as well as vaccines as a means of standardizing quality assurance began to take hold in the tail end of the 20th Century. The idea came together at the meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2001.¹⁵⁴⁸ WHO Prequalification would have particular implications for the *International Pharmacopoeia*; given the longstanding focus of the *International Pharmacopoeia* on Essential Medicines, explicitly linking it to WHO Prequalification ensured that the development of new monographs would impact the practical needs of specific disease programmes and the Essential Medicines they utilized.¹⁵⁴⁹ In turn, drug prequalification standards were developed with the purpose of guiding the purchasing practices of UN

¹⁵⁴⁴ WHO Expert Committee on Biological Standardization. Procedure for evaluating the acceptability in principle of vaccines proposed to United Nations agencies for use in immunization programmes. Technical Report Series 760. (Geneva: 1987).

¹⁵⁴⁵ Dellepiane, Nora & David Wood, "Twenty-five years of the WHO vaccines prequalification programme (1987-2012): lessons learned and future perspectives" (2015) 33:1 Vaccine 52–61.

¹⁵⁴⁶ World Health Assembly, "Immunization and Vaccine Quality" (13 May 1992) WHA45.17.

¹⁵⁴⁷ See e.g., Hoen, Ellen F M 't et al., "A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme" (2014) 35:2 J Public Health Policy 137–161.

¹⁵⁴⁸ World Health Organization, ed, *Thirty-seventh report / WHO Expert Committee on Specifications for Pharmaceutical Preparations: Geneva, 22 - 26 October 2001*, WHO technical report series 908 (Geneva: World Health Organization, 2003).

¹⁵⁴⁹ World Health Organization, ed, *Thirty-seventh report / WHO Expert Committee on Specifications for Pharmaceutical Preparations: Geneva, 22 - 26 October 2001*, WHO technical report series 908 (Geneva: World Health Organization, 2003).

agencies, with the Expert Committee adopting the “Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies”.¹⁵⁵⁰ Outside the UN, public/private bodies like the Global Fund for HIV/AIDS, Tuberculosis and Malaria also quickly embraced WHO Prequalification.¹⁵⁵¹ This widespread adoption was also reflected in volume; by 2008, 85-88 per cent of the ARVs procured by the Global Fund, UNITAID, and PEPFAR (the President’s Emergency Plan for AIDS Relief, an American aid mechanism) were WHO prequalified.¹⁵⁵²

WHO Prequalification does not yet encompass the full range of Essential Medicines; however, Essential Medicines for Neglected Diseases account for a disproportionate number of those that have received WHO Prequalification. This is further reason why this mechanism should be of interest to Canada and other HICs facing challenges accessing such drugs. While initially prequalification focused on HIV, it was followed quickly by multiple drugs for TB and malaria. Within the first decade, WHO Prequalification encompassed additional products, including for reproductive health. This expansion would also include the first prequalified NTD drug: diethylcarbamazine, a long off-patent Essential Medicine used to treat lymphatic filariasis, and once approved but long discontinued in markets like the US and Canada.¹⁵⁵³ Today, the number of prequalified drugs has expanded even further, while diagnostics and vector control tools are also eligible for

¹⁵⁵⁰ World Health Organization, ed, *Thirty-seventh report / WHO Expert Committee on Specifications for Pharmaceutical Preparations: Geneva, 22 - 26 October 2001*, WHO technical report series 908 (Geneva: World Health Organization, 2003).

¹⁵⁵¹ The Global Fund, “Guide to Global Fund Policies on Procurement And Supply Management of Health Products” (November 2020), online: <https://www.theglobalfund.org/media/5873/psm_procurementsupplymanagement_guidelines_en.pdf>.

¹⁵⁵² Hoen, Ellen F M ‘t et al., “A quiet revolution in global public health: The World Health Organization’s Prequalification of Medicines Programme” (2014) 35:2 J Public Health Policy 137–161.

¹⁵⁵³ Zyl, AJ van, “WHO prequalification of medicines programme: ensuring quality medicines: a decade of prequalification” (2011) 25:3 WHO Drug Information 231–239, online: <https://www.who.int/medicines/technical_briefing/tbs/vz1.pdf>. Diethylcarbamazine was discontinued in Canada in 2000.

prequalification.¹⁵⁵⁴ As of April 2022, over 600 prequalified medicine products were listed on the WHO website.¹⁵⁵⁵ This included 123 products for TB, 84 for malaria, and 9 (constituting 6 different drugs) for Neglected Tropical Diseases; numerous additional products in all categories are currently being assessed for prequalification.¹⁵⁵⁶ Half of the NTD drugs available from prequalified sources are currently unmarketed in Canada, while virtually all of the Essential Medicines for TB and malaria currently absent from the Canadian market have one or more manufacturers.

This illustrates how, when it comes to Essential Medicines with small markets in HICs, the opportunity offered by WHO Prequalification means it should not be overlooked, or mistaken for a tool solely for LMICs. SRAs and WHO Prequalification are already widely considered equivalent at the international level; it is time to move towards accepting it as such at the national level as well, at least for off-patent Essential Medicines that are not going to come to market via traditional channels in any case. While broader policy questions remain about balancing the pros and cons of accepting foreign or international standards for pharmaceuticals in general, accepting WHO Prequalification alongside other SRAs for otherwise unmarketed off-patent Essential Medicines for Neglected Diseases is a clear improvement over the status quo in Canada. Furthermore, rather than opening the floodgates to foreign sources and fears of potential quality concerns, the limited pool of such drugs is well-suited to piloting a narrow new mechanism for formal market entry while Canada adjusts to accepting global standards. There are other advantages; for instance, focusing on important unmarketed drugs avoids the argument that accepting these standards as sufficient for Canadian approval

¹⁵⁵⁴ While beyond the scope of this thesis, vector control in particular has major implications for numerous Neglected Diseases, including Chagas disease, visceral leishmaniasis, and African trypanosomiasis, as well as malaria, lymphatic filariasis, and other mosquito-borne diseases.

¹⁵⁵⁵ For clarity, some of these products are the same drug in different forms or dosages, or made by different manufacturers. World Health Organization, WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control) online: <https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products>.

¹⁵⁵⁶ The six Essential Medicines for NTDs currently available are ivermectin, praziquantel, mebendazole, albendazole, diethylcarbamazine, and the new sleeping sickness drug fexinidazole, of which only the first three are available in Canada. Others, such as the anti-fungal flucytosine (not available in Canada) are under review.

gives new market entrants an unfair advantage over existing producers of the same drug.¹⁵⁵⁷ At the same time, this narrow approach also ensures that these medically important but commercially less appealing drugs do not get lost in the shuffle as new foreign-approved products enter the Canadian market.

It is true that deferring to another regulatory standard does pose some potential risks; however, as noted, Canada already lacks the enforcement capacity that other better resourced agencies, like the US FDA, possess for enforcing its standards around the world. For Essential Medicines that already form the global and domestic standard of care, the regulatory goals of safety and efficacy are generally met; accepting drugs meeting SRA or WHO Prequalification standards should address the third goal of quality. The idea of Canada pooling resources for inspections has been suggested elsewhere.¹⁵⁵⁸ Starting with a limited number of drugs also ensures that Canada has the opportunity to take practical, manageable steps to ensure its own regulatory priorities of safety, efficacy and quality are met. Such measures could be paired with federal procurement, as discussed earlier. For individual drugs, Canada has already *de facto* accepted WHO prequalified sources, even when alternatives from HIC SRAs were available. For instance, the Canadian Malaria Network's purchase of prequalified Chinese artesunate rather than the far more expensive FDA-approved artesunate offers a prime example of Canada opting for a WHO prequalified source over one from the United States, demonstrating that it is entirely possible to make such a choice in practice.

WHO Prequalification itself is still evolving.¹⁵⁵⁹ The Lancet Commission on Essential Medicines believes that "the WHO/UN Prequalification Programme can and should evolve to address a wider range of essential medicines, at least until international standards have been established and the global generic market has

¹⁵⁵⁷ A handful of Essential Medicines for Neglected Diseases – notably the DR-TB drugs bedaquiline and delamanid – are both still under patent and unmarketed in Canada. Ideally, these drugs would also be accessible from prequalified sources; however, the benefits of extending such a mechanism to patented drugs would need to be balanced against other legal considerations.

¹⁵⁵⁸ See e.g., Lee, Shoo K et al, "Pharmaceutical security for Canada" (2022) 194:32 CMAJ E1113–E1116.

¹⁵⁵⁹ This includes broader shifts towards classifying national regulatory authorities in general, something that was rapidly evolving as this thesis was being completed but is well beyond its scope.

developed sufficient capacity to produce and distribute adequate supplies of quality, safe medicines”.¹⁵⁶⁰ Given the focus on quality assurance, it would make sense to prioritize WHO Prequalification of Essential Medicines not currently available from any SRA, followed by Essential Medicines in short supply, and those that are unaffordable from existing sources by those who need them. To this end, potential benefits of supporting WHO Prequalification include not merely improved access to the particular drugs in question, but also broader capacity building within the countries where they are produced, a process stimulated by bringing together expertise from countries of different levels of regulatory prowess.¹⁵⁶¹ It should also be remembered that Canada itself has contributed not only financial support but technical expertise to the WHO Prequalification process.¹⁵⁶² Once again, it makes sense to reconcile Canada’s domestic and international goals in relation to access to medicines. By simultaneously providing support for WHO Prequalification and obtaining safe, effective, quality-assured Essential Medicines from WHO Prequalified sources, multiple Canadian goals both internationally and domestically could be satisfied at the same time.

The Global Drug Facility: An example of a pooled, prequalified drug supply

Recognition of WHO Prequalification offers not only domestic access to otherwise unmarketed drugs, particularly drugs that may not be available (or available at a reasonable price) from another SRA, but also furthers Canada’s broader geopolitical aspirations while helping tackle global concerns about access to high-quality Essential Medicines. As a prime example of how all these pieces could fit together, provided Canada is willing to take action, consider the Global Drug Facility (GDF). The GDF is a Canadian-supported international procurement mechanism overseen by the Stop TB Partnership; it relies upon WHO prequalified drugs. Over the past two decades, the GDF has proven very successful in providing

¹⁵⁶⁰ Wirtz, Veronika J et al. “Essential medicines for universal health coverage” (2017) 389:10067 *The Lancet* 403–476, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673616315999>>.

¹⁵⁶¹ Coyne, Philip E, “The World Health Organization Prequalification Programme—playing an essential role in assuring quality medical products” (2019) 11:2 *International Health* 79–80, online: <<https://academic.oup.com/inthealth/article/11/2/79/5245893>>.

¹⁵⁶² See e.g., World Health Organization, “Key Facts about the WHO Prequalification Project” (Undated), online: <<https://www.who.int/3by5/prequal/en/>>.

high quality tuberculosis drugs.¹⁵⁶³ Drugs obtained via the GDF meet WHO Prequalification or SRA standards; in turn, organizations like the Global Fund and USAID procure TB drugs from the GDF.

As noted earlier, TB drugs, particularly DR-TB drugs like cycloserine, have been particular targets for WHO Prequalification. Unlike for HIV, prequalification for TB drugs was not initially about ensuring broader access to cheaper versions of patented drugs (although this has since become relevant for new drugs like bedaquiline and delamanid). Of greater initial importance was ensuring a sustainable, affordable global supply of quality-assured off-patent drugs. This included not only first-line drugs for drug-sensitive TB, but drugs for drug-resistant TB. Previously, with a fragmented, decentralized global market, even off-patent drugs for DR-TB were frequently expensive, including in many LMICs.¹⁵⁶⁴ In turn, DR-TB, as highlighted earlier, is also the most prominent intersection of AMR, Neglected Diseases, and access to Essential Medicines; erratic or unaffordable supplies can be particularly serious for TB, driving drug resistance that makes treatment more difficult and in turn increases public health risks.¹⁵⁶⁵ Drug resistance is impacted not only by issues of access – in terms of both physical availability and affordability – to the right drugs, but also issues of access to drugs of sufficient quality.¹⁵⁶⁶ As such, sustainable, affordable access to high-quality drugs is a necessary component of the global response to TB. To tackle these issues, the GDF was created in 2001 at the same time the broader concept of WHO Prequalification for drugs was emerging.

One of the often-overlooked steps in the development of the GDF was a proactive effort to ensure that effective DR-TB drugs were added to the WHO

¹⁵⁶³ See e.g., Hauk, Cathrin et al., “Quality assurance in anti-tuberculosis drug procurement by the Stop TB Partnership—Global Drug Facility: Procedures, costs, time requirements, and comparison of assay and dissolution results by manufacturers and by external analysis” (2020) 15:12 PLoS ONE e0243428, online: <<https://dx.plos.org/10.1371/journal.pone.0243428>>.

¹⁵⁶⁴ See e.g., White, V L C, “Resource implications of patients with multidrug resistant tuberculosis” (2000) 55:11 Thorax 962–963, online: <<https://thorax.bmj.com/lookup/doi/10.1136/thorax.55.11.962>>.

¹⁵⁶⁵ Kumaresan, J et al., “The Global TB Drug Facility: innovative global procurement” (2004) 8:1 Int J Tuberc Lung Dis 130–138.

¹⁵⁶⁶ Caminero, J A, “Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding” (2010) 14:4 Int J Tuberc Lung Dis 382–390.

MEML in the first place. At an expert meeting in 1999, before the GDF or even WHO Prequalification for medicines came into their own, the value of explicitly recognizing these vital DR-TB drugs as Essential Medicines was recognized as one of the key barriers to global access:

[WHO representative] Dr. Evans reaffirmed the importance of the Model List of Essential Drugs in vaccine procurement, and reiterated the importance of including secondline antituberculous drugs on the list. About 145 countries construct their national formularies based on the WHO list, and absence of a drug from the WHO list makes its registration virtually impossible in many cases. Countries without well-funded regulatory authorities rely especially heavily on the WHO list, since it provides assurance that drugs included are “right by science,” and that treatment guidelines exist.¹⁵⁶⁷

The WHO MEML draws upon WHO treatment guidelines and similar reference materials; in turn, both the MEML and WHO guidance help influence many countries in determining what drugs are needed in their domestic programs and how to use them. Identifying these DR-TB drugs as Essential Medicines helped guide a standardized international list of medicines shared across individual countries, while also establishing a more predictable global market for these drugs. Meanwhile, the *International Pharmacopoeia* draws upon the WHO MEML to set standards for key Essential Medicines. In turn, the *International Pharmacopoeia* helps guide the production of quality-assured drugs through WHO Prequalification. Providing a list of effective drugs, available of assured quality and at an affordable

¹⁵⁶⁷ Gupta, R et al., Proceedings from the Procurement of Second-Line Anti-Tuberculosis Drugs for DOTS-Plus Pilot Projects, Cambridge, MA, 5 to 6 July 1999, R. Gupta et al., Eds. (WHO, Geneva, 2000). Here we do see countries with limited resources using the WHO MEML as a ceiling rather than a floor; however, as noted, use of the WHO MEML as a guideline for triage in environments with limited resources is different from doing so in a context where resources are abundant. Furthermore, many of these same drugs then absent from the WHO MEML remain unavailable in Canada even after their inclusion on the MEML, underscoring how worries about a ceiling tied to slavish adherence to the MEML have historically been misplaced in HICs.

price, thus simplifies drug management in and across countries.¹⁵⁶⁸ The GDF facilitates this by providing a centralized mechanism for securing and supplying drugs from WHO prequalified and SRA sources. This helps further stabilize the global market, in terms of both price and availability.

The GDF also provides further illustration of how WHO Prequalification could help address barriers to accessing off-patent Essential Medicines in countries like Canada, as well as how Canada's use of such a mechanism could simultaneously help reinforce WHO Prequalification efforts. Canadian funding underpinned the creation of the GDF in 2001, and Canada has consistently been a major, and at times the single biggest, source of funding for the Facility.¹⁵⁶⁹ To see what the GDF could offer Canada in return, consider a by-now familiar drug: Cycloserine. In the fall of 2015, at the same time that the 5000% price hike by Rodelis in the United States spilled over into Canada via the SAP and drove the price up to over \$350 USD per pill, a package of 100 250mg capsules of cycloserine could be obtained from the GDF for between \$19.45 and \$26.80 USD according to the GDF's then-current catalogue (as of April 2021, the same package is listed at between \$21.00 and \$25.90 USD).¹⁵⁷⁰ These prices for a drug not formally available in Canada are possible in part thanks to Canada's support.

It makes little sense that an old, off-patent Essential Medicine for DR-TB that Canada helps ensure is available around the world at pennies per pill, with assurances of quality based on the same *International Pharmacopoeia* standards that Canada explicitly recognizes in its own *Food and Drugs* legislation, can only be obtained in Canada through an indirect, unreliable mechanism designed for new or experimental medications. It makes even less sense for Canada to continue its current approach of obtaining these unmarketed TB drugs from SRAs when doing so has come at a financial cost, in the case of cycloserine, of over 1000 times the

¹⁵⁶⁸ Kumaresan, J et al., "The Global TB Drug Facility: innovative global procurement" (2004) 8:1 Int J Tuberc Lung Dis 130–138.

¹⁵⁶⁹ See e.g., Stop TB Partnership. "Canadian-Funded Drug Facility Proves Major Success In Global Fight Against Tuberculosis", *Press Release* (24 March 2005), online: <http://www.stoptb.org/events/world_tb_day/2005/assets/PDF/Stop%20TB%20Press%20Release%20English.pdf>.

¹⁵⁷⁰ Global Drug Facility, *April 2021 Medicines Catalog*, (Stop TB Partnership) online: <<http://www.stoptb.org/assets/documents/gdf/drugsupply/GDFMedicinesCatalog.pdf>>.

GDF price. Still, Canada, like other high-income countries, has long been “assumed to have the resources and infrastructure necessary to maintain continuous availability of suitable anti-tuberculosis medications” even where this has demonstrably not been the case.¹⁵⁷¹ This remains true even though use of the GDF by high-income countries is not discouraged; in fact, the Political Declaration coming out of the UN General Assembly High-Level Meeting on tuberculosis in 2018 was explicit in making the opposite point. Per the Declaration, participating states:

Recognize the role played by the Stop TB Partnership/ Global Drug Facility, which has, since its creation in 2001, increased access to high-quality and affordable tuberculosis treatment and diagnostics for populations in need and is *open as an option to be considered for use by all nations, and therefore encourage all nations to use the Stop TB Partnership/ Global Drug Facility [emphasis added]*.¹⁵⁷²

There are further advantages to high-income countries like Canada drawing upon the GDF, as recommended in the Political Declaration. First, pooled orders through the GDF help to ensure a more sustainable global supply; countries making purchases for domestic use can thus reinforce global supply. This could well be self-reinforcing in other ways too; getting a return on its investment – access to quality-assured medicines it otherwise lacks – offers an incentive for Canada to continue, or indeed increase, its support for mechanisms like the GDF. Generally, HICs like Canada will also require relatively small quantities of many of these drugs, enough to contribute to a sustainable global market but not enough to interfere with sufficient supply for other countries.¹⁵⁷³ Furthermore, participation by high-income countries sends a signal that prequalified medicines are not

¹⁵⁷¹ Capstick, T G D et al., “Treatment interruptions and inconsistent supply of anti-tuberculosis drugs in the United Kingdom” (2011) 15:6 Int J Tuberc Lung Dis 754–760.

¹⁵⁷² United Nations General Assembly, *Political Declaration of the UN General Assembly High-Level Meeting*, by United Nations General Assembly, Resolution A/RES/73/3 (2018).

¹⁵⁷³ This is distinct from the situation of, say, COVID-19 vaccine hoarding, where HICs outcompeted LMICs for large amounts of scarce goods.

second-class drugs; what is good enough for WHO Prequalification is good enough for Canada, and in turn for the world at large.

Even once it is accepted that Canada should draw drugs from the GDF, however, the question remains how such drugs would be accessed. If Canada is not yet ready to take the step of accepting WHO Prequalification as equivalent to formal approval, it could at least expand existing measures to access unmarketed drugs to encompass WHO Prequalified medicines. One simple step in this regard would be to expand the list of accepted authorities under the SAP and the UPHN to include WHO Prequalification. This would not solve all the problems of the SAP, but it would help to ameliorate some of them. However, to best facilitate access, Canada should not settle for unmarketed drugs. As discussed above, WHO Prequalification should be accepted for the purposes of formal market entry, at least for certain otherwise unmarketed drugs. Off-patent Essential Medicines absent from the market make sense as an initial foray into Canadian acceptance of WHO Prequalification for a range of reasons. They are drugs that are unavailable despite their utility being recognized in a Canadian context; they are a logical choice in terms of aligning Canada with international norms and obligations around Essential Medicines; and restricting initial forays in this area to unmarketed, off-patent Essential Medicines minimizes any risk of conflict with either patent holders or disgruntled competitors who underwent the traditional route to market. Most importantly, they fill an important health need. If deemed necessary, such approval could be framed as a new pathway, akin to the EUNDS, that accepts foreign standards in recognition of the challenges of bringing particular drugs to market. This pathway could be accompanied by targeted requirements, ranging from reporting obligations for physicians to quality testing of samples (this latter option readily paired with centralized federal procurement). All of this could in turn serve as a testing ground for acceptance of international standards; if successful, it may well be logical to expand the remit of such a program to other drugs, though the outer boundaries of what might ultimately be included fall outside of this thesis. This is not a complete solution, of course. Some of these drugs may still not be sufficiently commercially appealing. Here, additional measures may need to be

taken. For instance, rather than waiting for manufacturers to come to Canada, active procurement by the federal government could proactively seek out drugs identified as important as a consequence of Canada's process of developing a Canadian EML.

Despite a dearth of concrete action until recently, Canada boasts a lengthy history of at least talking about harmonizing international standards and recognizing foreign drug reviews directly.¹⁵⁷⁴ To this end, Canada participates in international groups like the Global Harmonization Task Force (GHTF) and the International Conference on Harmonisation (ICH). Canada also has binding agreements with other countries in relation to various standards for pharmaceuticals; as one illustrative example, the Canada/EU trade agreement (Comprehensive Economic and Trade Agreement – CETA) includes a protocol on the mutual recognition of the compliance and enforcement programme regarding good manufacturing practices for pharmaceutical products.¹⁵⁷⁵ More recently, in addition to the specific examples discussed earlier in this thesis where Canada is already relying on foreign regulatory bodies in limited circumstances – the UPHN, the reformed SAP, interim orders in response to COVID-19 shortages – there are signs Canada is increasingly open to accepting foreign regulatory standards. Indeed, as this thesis was being finalized, there were announcements of a regulatory initiative, “Regulations Amending the Food and Drug Regulations - Use of Foreign Decisions (UFD) Pathway” whose brief description suggests that through

¹⁵⁷⁴ See e.g., World Health Assembly, “Clinical and Pharmacological Evaluation of Drugs” (1962) WHA15.41, a resolution that was, according to Canada's Minister of National Health & Welfare, initiated and co-sponsored by Canada in the wake of thalidomide “to promote greater international co-operation in the drug field, and particularly to secure regular exchange of information on the safety and efficacy of pharmaceutical preparations”. Statement by Jay Waldo Monteith, October 26, 1962 (25th Parliament, 1st Session), online: <<https://www.lipad.ca/full/permalink/2183142/>>; Health Canada, “Draft guidance document: The use of foreign reviews by Health Canada”, (11 September 2012), online: <<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/use-foreign-reviews/draft-use-foreign-reviews-health-canada-revisions-use-foreign-reviews-pilot-project.html>>.

¹⁵⁷⁵ Global Affairs Canada, “Text of the Comprehensive Economic and Trade Agreement – Protocol on the mutual recognition of the compliance and enforcement programme regarding good manufacturing practices for pharmaceutical products” (2017), online: <<https://www.international.gc.ca/trade-commerce/trade-agreements-accords-commerciaux/agr-acc/ceta-aecg/text-texte/P3.aspx>>.

"a streamlined application pathway that allows manufacturers to rely on the authorization of a trusted foreign regulator, Health Canada is aiming to facilitate access to certain drugs that address an unmet medical need".¹⁵⁷⁶ More specifically:

This pathway would be suitable for drugs that have not yet received market authorization for the Canadian market. It would be used for a sub-set of drugs that have been authorized by specified foreign regulators, have an adequate amount of post-market experience, and meet internationally established food safety standards for certain veterinary drugs. For human drugs, this pathway could be used for prescription drugs such as those on the Special Access Program (SAP) or those listed on the Urgent Public Health Needs (UPHN) List.¹⁵⁷⁷

Little further information is available at this time, although the webpage notes that the temporary measures via which Health Canada leveraged foreign regulatory decisions in the authorization of COVID-19 products "will help inform the policy approach for this proposal".¹⁵⁷⁸ A regulatory proposal was tentatively planned for public comment in spring 2022, though it had not materialized as of completion of this thesis.¹⁵⁷⁹ At the risk of appearing overly optimistic after years of stagnancy punctuated by bursts of at best limited progress, this description sounds like it has the potential to address many of the key issues at hand. Off-patent Essential

¹⁵⁷⁶ Health Canada, "Forward Regulatory Plan 2021-2023: Regulations Amending the Food and Drug Regulations - Use of Foreign Decisions (UFD) Pathway" (4 April 2021), online: <<https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/plan/use-foreign-decisions-pathway.html>>.

¹⁵⁷⁷ Health Canada, "Forward Regulatory Plan 2021-2023: Regulations Amending the Food and Drug Regulations - Use of Foreign Decisions (UFD) Pathway" (4 April 2021), online: <<https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/plan/use-foreign-decisions-pathway.html>>.

¹⁵⁷⁸ Health Canada, "Forward Regulatory Plan 2021-2023: Regulations Amending the Food and Drug Regulations - Use of Foreign Decisions (UFD) Pathway" (4 April 2021), online: <<https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/plan/use-foreign-decisions-pathway.html>>.

¹⁵⁷⁹ Health Canada, "Forward Regulatory Plan 2021-2023: Regulations Amending the Food and Drug Regulations - Use of Foreign Decisions (UFD) Pathway" (4 April 2021), online: <<https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/plan/use-foreign-decisions-pathway.html>>.

Medicines would certainly seem to meet the description of the drugs in question. However, the identity of the “specified foreign regulators” will impact the result; as seen throughout this thesis, certain Essential Medicines for Neglected Diseases might be exploitatively priced, or completely unavailable, in HICs, indicating the need for other sources. The status of WHO Prequalification in particular remains ambiguous within the context of the proposal at this time; as discussed above, recognizing the niche that WHO Prequalification fills would be to Canada’s benefit, as well as the world’s. Furthermore, simply identifying a list of foreign regulators is not enough. Passive recognition of other jurisdictions as a path to Canadian market entry will still depend on active participation by manufacturers approved there; this may benefit access to commercially appealing drugs, but it won’t address all the Essential Medicines at the core of this thesis. Instead, through engagement with the WHO MEML and other reference points, Canada should be actively identifying a list of unmarketed medicines already constituting the standard of care in Canada, then asking how their safety, efficacy and quality can be assured, and what proactive steps can be taken to ensure access.

A domestic role in the international market

When it comes to off-patent Essential Medicines for Neglected Diseases, accessing those drugs in a way that helps stabilize the global market and furthers Health Canada’s goals of safety, efficacy and quality while also strengthening regulatory standards at the international level seems a sensible approach for Canada. All that said, particularly in the wake of border closures that disrupted trade in pharmaceuticals both unintentionally and intentionally during the COVID-19 pandemic, there are reasons to think about domestic production. Domestic production also involves identifying what drugs to produce.¹⁵⁸⁰ Indeed, the first American list of “Essential Medicines” was created under these circumstances for just this purpose.¹⁵⁸¹ COVID-19 has similarly prompted Canada to invest in its own

¹⁵⁸⁰ See e.g., Lee, Shoo K et al, “Pharmaceutical security for Canada” (2022) 194:32 CMAJ E1113–E1116.

¹⁵⁸¹ President of the United States, Executive Order 13944 of August 6, 2020, “Combating Public Health Emergencies and Strengthening National Security by Ensuring Essential Medicines, Medical

pharmaceutical manufacturing sector, particularly for goods like vaccines that it proved in practice unable to produce domestically. Such measures, including investment in manufacturing, form part of Canada's Biomanufacturing and Life Sciences Strategy.¹⁵⁸²

Some elements of the strategy go beyond influencing private producers to implementing an expanded role for public production. Such plans, particularly for publicly owned manufacturing facilities, would seem to reflect the calls, noted earlier, for a return to the allegedly halcyon days of Connaught Labs. However, the rosy-hued view sometimes espoused of Connaught Laboratories is a history that never quite existed in reality. A complete history of Connaught Labs is beyond the scope of this thesis, though some of its early years were recounted earlier. However, the idea that Canada ever had a government-run pharmaceutical company producing medicines purely as a public good is something of a myth. Groundbreaking work was conducted at Connaught Labs, particularly in its early decades, but it was never a purely state-owned and state-directed pharmaceutical company in Canada producing drugs at non-profit prices. Much of its most famous work came in its initial decades as part of the University of Toronto. In 1972, it was sold by the University of Toronto to the Canada Development Corporation, a public/private entity established by statute the year before.¹⁵⁸³ Contrary to common assumptions around government involvement in pharmaceutical production, the objects of the Canada Development Corporation were explicitly profit-driven on behalf of its public and private shareholders.¹⁵⁸⁴ Choices made in pursuit of this profit orientation in turn led to criticisms more often associated with purely private companies: that it was not investing in R&D or the infrastructure necessary to conduct it, and that it was not sufficiently safeguarding Canada's

Countermeasures, and Critical Inputs Are Made in the United States" (2020) 85:158 *Federal Register*.

¹⁵⁸² Science and Economic Development Canada, *Canada's biomanufacturing and life sciences strategy* (2022), online: <[https://www.ic.gc.ca/eic/site/151.nsf/vwapj/1098_01_21_Biomanufacturing_Strategy_EN_WEB.pdf/\\$file/1098_01_21_Biomanufacturing_Strategy_EN_WEB.pdf](https://www.ic.gc.ca/eic/site/151.nsf/vwapj/1098_01_21_Biomanufacturing_Strategy_EN_WEB.pdf/$file/1098_01_21_Biomanufacturing_Strategy_EN_WEB.pdf)>.

¹⁵⁸³ *An Act to establish the Canada Development Corporation*, C-219 (1971).

¹⁵⁸⁴ *An Act to establish the Canada Development Corporation*, C-219 (1971), s.6.

access to necessary products.¹⁵⁸⁵ These concerns were being voiced even before its assets were privatized and controversially sold to France's Institut Mérieux SA in 1989, raising a further chorus of concern about Canada's control over what products were manufactured and for what purpose.¹⁵⁸⁶ At the same time, it should also be noted that Canada did not physically lose the privatized facilities. To this day, these facilities are still operated by Sanofi to make vaccines.¹⁵⁸⁷ The same is true for the vaccine production facilities of the Institut Armand Frappier at the University of Québec in Montréal, which are today owned by GSK.¹⁵⁸⁸ Ironically, as of the submission of this thesis, a joint collaboration between Sanofi and GSK to produce a COVID-19 vaccine had yet to yield an approved final product.¹⁵⁸⁹

As this suggests, privately-owned capacity in Canada is not the same as no capacity, but it also differs from state-owned or controlled capacity; as Canada spends more on developing both public and private capacity in the wake of COVID-19, questions remain about how much influence it will exert in exchange for that funding. This broader debate is beyond the scope of this thesis.¹⁵⁹⁰ However, a related consideration is the question of what Canada will do with its renewed manufacturing capacity, be it state-owned or state-influenced, in between

¹⁵⁸⁵ See e.g., "CMA committee report on Connaught Laboratories Ltd" (1977) 116:1 Can Med Assoc J 67–70.

¹⁵⁸⁶ See e.g., Ferguson, Jonathan, "Canadians don't want to fund a 'treasure' like Connaught" *Toronto Star* (30 September 1989); Newman, Peter C, "Lament for a cherished asset" *Maclean's* (16 October 1989), online: <<https://archive.macleans.ca/article/1989/10/16/lament-for-a-cherished-asset>>.

¹⁵⁸⁷ For an op-ed adopting this opposing stance, see Mayer, Charlie, "Privatized Connaught Labs is still going strong", *Financial Post* (10 December 2020), online: <<https://financialpost.com/opinion/charlie-mayer-privatized-connaught-labs-is-still-going-strong>>.

¹⁵⁸⁸ Forani, Jonathan, "'We took our eye off the ball': How Canada lost its vaccine production capacity", *CTV News* (25 November 2020), online: <<https://www.ctvnews.ca/health/coronavirus/we-took-our-eye-off-the-ball-how-canada-lost-its-vaccine-production-capacity-1.5204040>>; Tasker, John Paul, "Vaccine envy: Why can't Canada make COVID-19 doses at home?", *CBC News* (28 April 2021), online: <<https://www.cbc.ca/news/politics/domestic-vaccine-manufacturing-canada-1.6004427>>.

¹⁵⁸⁹ Sanofi, "Sanofi and GSK to seek regulatory authorization for COVID-19 vaccine", (23 February 2022), online: <<https://www.sanofi.com/en/media-room/press-releases/2022/2022-02-23-11-15-00-2390091>>.

¹⁵⁹⁰ The author of this thesis has argued in other contexts both for attaching strings to such funding, and increased transparency around strings attached to public funding. See e.g., Médecins Sans Frontières, "Written Submission for the Pre-Budget Consultations in Advance of the Upcoming Federal Budget" (August 2021), online: <https://www.doctorswithoutborders.ca/sites/default/files/submission_from_doctors_without_borders_-_2022_pre-budget_consultation_submission.pdf>.

pandemics. If the goal is to have sufficient capacity ready for the next pandemic, something will need to be manufactured to keep facilities active. Here, the arguments for public manufacturing of a widely used Essential Medicine – insulin seems an appropriate choice of example in Connaught’s shadow – would be considerably different than those for small niches that might be measured in tens of patients.¹⁵⁹¹

Truth be told, when it comes to state production, targeting off-patent Essential Medicines for Neglected Diseases like cycloserine and albendazole may not be a particularly effective use of manufacturing capacity. It is true that in cases where the market does not supply such products at all, government production would not face the same criticisms as it would if competing with private industry. However, while state production of an otherwise unmarketed drug might yield societal benefits, it is not clear that those benefits would always be sufficient to justify the effort, particularly if that production were geared to domestic consumption. This is all the more the case where the state might also have to produce its own API. Producing just enough cycloserine – a drug required by a handful of patients, albeit urgently, each year – to meet Canada’s domestic needs would be highly inefficient. This is particularly true when alternatives such as accessing a quality-assured pooled supply like the GDF that Canada is already financially invested in is a ready – if as yet unexercised – alternative. Regardless of the potential merits of state manufacture of pharmaceuticals in general, including as a means of asserting domestic control and promoting pharmaceutical sovereignty, attempting to publicly manufacture all of the unmarketed drugs discussed in this thesis in the quantities necessary for the Canadian market is a poor use of resources, both for improving access to those particular drugs, and for the health system in general. At the same time, however, there could still be a valuable role for state manufacturing of off-patent Essential Medicines for Neglected Diseases in Canada, one complementary to expanded Canadian

¹⁵⁹¹ Of course, “insulin” as a catch-all term covering everything from the original animal insulins to more recent synthetic insulins is itself a different matter than a century ago.

recognition of foreign standards and active participation in mechanisms like the GDF.

Rather than make small amounts of numerous drugs (and potentially their APIs), it would make more sense for any Canadian forays into production of Essential Medicines for Neglected Diseases to focus on a smaller number of drugs, but in turn produce them in quantities sufficient to help fill gaps in the global supply. This would be a part of the Connaught legacy worth embracing. As detailed earlier, the global need for products Canada exported during the Connaught era, such as DAT, exceeds current global production.¹⁵⁹² Indeed, many of the Essential Medicines for Neglected Diseases highlighted in this thesis would benefit from production geared not at generating profits, but maintaining a stable, affordable supply of important tools used to achieve global health goals. Global recognition of Canada as a Stringent Regulatory Authority would help instill confidence in Canada's products. These could be sold in some markets, and potentially donated in others. This would be an opportunity to look outward as well as inward when it comes to domestic production capacity. Given that Canada requires small amounts of these drugs for its own use, is highly unlikely under any circumstances to produce all the Essential Medicines not currently sold in Canada, and faced numerous access barriers well before COVID-19, this is an area where placing too much emphasis on the security of domestic supply would be misplaced. By contrast, emphasizing other benefits of this investment would pay off in other ways.

Supplying the world with certain important drugs at risk of vanishing from global markets entirely could help burnish Canada's global health credentials, particularly following their tarnishing around vaccine nationalism and COVID-19 vaccines.¹⁵⁹³ To reiterate, such a role would not involve Canada producing all the Essential Medicines it currently lacks; however, it would involve Canada feeding into a global system of quality-assured Essential Medicines that it would draw from

¹⁵⁹² Acknowledging the particular difficulties of manufacturing DAT using the existing method.

¹⁵⁹³ See e.g., Houston, Adam R & Srinivas Murthy, "Canada is no global health leader on COVID-19 vaccine equity" (2021) 397:10287 *The Lancet* 1803, online: <<https://linkinghub.elsevier.com/retrieve/pii/S0140673621008886>>.

in return. This would at last help to align Canada's approach to Essential Medicines for Neglected Diseases abroad with its approach at home. It would also help Canada meet its legal and normative obligations towards other states, particularly states with fewer resources.

In closing, there is one last cautionary tale regarding a previous Canadian attempt to produce Essential Medicines for export, which should serve as a reminder of how not to go about this. This is Canada's Access to Medicines Regime (CAMR), a well-meaning and (technically) world-beating, yet ultimately woefully unsuccessful effort by Canada to play a role in ensuring access to medicines in countries without domestic pharmaceutical production capacity. Established via the modestly named *Jean Chrétien Pledge to Africa Act* in 2004, CAMR was an attempt to domestically operationalize flexibilities under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) of the World Trade Organization.¹⁵⁹⁴ The CAMR story is a long and contentious one beyond the scope of this thesis.¹⁵⁹⁵ Often overlooked, however, is how it illustrates once again the disjunct between Canada's approach towards Essential Medicines at home and abroad.

To become eligible for CAMR, a drug must be listed on Schedule 1 of the *Patent Act*. As described in the legislative summary accompanying the *Jean Chrétien*

¹⁵⁹⁴ *An Act to amend the Patent Act and the Food and Drugs Act (The Jean Chrétien Pledge to Africa)*, SC 2004, c 23.

¹⁵⁹⁵ In brief, CAMR is a framework within s.21.01-21.19 of the *Patent Act* (R.S.C., 1985, c. P-4). It permits compulsory licensing of patented medicines expressly for export to countries without the domestic manufacturing capacity that would permit them to exercise a compulsory license themselves. These measures, particularly the exercise of compulsory licences on behalf of countries without domestic production capacity, had been a key outcome of the WTO's Doha Declaration. Doha WTO Ministerial 2001: Ministerial Declaration WT/MIN(01)/DEC/1 20 Nov. 2001 ("*Doha Declaration*"). Paragraph 6 of the Doha Declaration was subsequently codified as Article 31bis of the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). *Agreement on Trade-Related Aspects of Intellectual Property Rights*, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994). Despite bold aspirations, CAMR was only ever used once, to send two shipments of an antiretroviral drug to Rwanda. At the same time, this rather underwhelming showing by CAMR remains the only time any country in the world has successfully used this TRIPS flexibility, making it simultaneously the most and least successful case study. As one recent pre-COVID-19 example from the CAMR literature, with an extensive bibliography of other scholarly work, see Houston, Adam R & Reed F Beall, "Could the Paragraph 6 Compulsory License System be Revised to Increase Participation by the Generics Industry? Lessons Learned from an Unheralded and Unsuccessful Attempt to Use Canada's Access to Medicines Regime" (2019) McGill JL & Health 12:2.

Pledge to Africa Act, the initial list of eligible products on Schedule 1 consisted of “all products on the World Health Organization’s (WHO) list of essential medicines that are currently under patent in Canada”.¹⁵⁹⁶ This link to the WHO MEML has been highlighted as demonstrating Canada’s recognition of the global importance of Essential Medicines.¹⁵⁹⁷ Indeed, the fact that certain drugs were *not* included on the WHO MEML at the time was leveraged by pharmaceutical companies to keep them off the inaugural version of Schedule 1.¹⁵⁹⁸ At the same time, the drafting of the initial list managed to cast a very wide net, with Schedule 1 ensnaring products whose blanket patent status seems exceedingly dubious, ranging from diphtheria vaccine to morphine.¹⁵⁹⁹ In doing so, it also inadvertently demonstrated gaps in Canada’s own access to Essential Medicines for Neglected Diseases; Schedule 1 included – and still includes – Essential Medicines that had already disappeared from the Canadian market (like diphtheria antitoxin) and others that had not been brought to the Canadian market at the time (like ivermectin). Any Canadian approach to manufacturing Essential Medicines needs to take into account domestic and global needs. The next step is to determine not merely which Essential Medicines Canada needs, but which Essential Medicines need Canada.

¹⁵⁹⁶ Acharya, Lalita & Kristen Douglas, “Bill C-9: An Act to Amend the Patent Act and the Food and Drugs Act Legislative Summary” (Library of Parliament, 2004).

¹⁵⁹⁷ Eom, Gina, Paul Grootendorst & Jacalyn Duffin. “The case for an essential medicines list for Canada” (2016) 188:17–18 CMAJ E499–E503, online: <<http://www.cmaj.ca/lookup/doi/10.1503/cmaj.160134>>.

¹⁵⁹⁸ In the lead-up to the passage of the *Jean Chrétien Pledge to Africa Act*, there was initial agreement among Parliamentary committee members to add two further drugs to Schedule 1 that were not on the WHO MEML at the time (moxifloxacin and clarithromycin; both have since been added to the MEML, the former for drug-resistant TB). Elliott, Richard, “Delivering on the Pledge: Global Access to Medicines, WTO Rules, and Reforming Canada’s Law on Compulsory Licensing for Export” (2007) 3:1 McGill Journal of Sustainable Development Law. Behind the scenes, however, Bayer, the maker of moxifloxacin, actually contacted MPs to convince them not to include the drug under Schedule 1. McGregor, Glen, “Drug bill lets ‘Big Pharma’ call the shots”, *The Ottawa Citizen* (4 May 2004). Subsequently, in the House of Commons itself, motions brought forward by the NDP to add these two drugs to Schedule 1 were opposed by other parties, including the governing Liberals; the primary reason cited for their opposition was that neither of these drugs were on the WHO MEML. Hansard, 37TH Parliament, 3rd Session. No. 043 (Wednesday, April 28, 2004). See in particular the debate lines 1655-1725, online: <<https://www.ourcommons.ca/DocumentViewer/en/37-3/house/sitting-43/hansard>>.

¹⁵⁹⁹ This is but one example of the bizarre drafting in Schedule 1. Other broad inclusions include “hepatitis B vaccine” and “potassium chloride powder for solutions”. This is not to suggest no patents on any version of any of these drugs existed, but it is unclear why off-patent forms could not be produced.

Conclusion

The most important conclusion is one that has been apparent from the opening pages: Canadian patients should have access to Essential Medicines recognized both nationally and internationally as the standard of care. It is neither logical nor acceptable that Essential Medicines which are among the most basic health interventions in low-income settings are not formally available in a wealthy country that embraces universal healthcare as part of its national identity. Indeed, Canada has already demonstrated it is capable of directing considerable resources towards getting important medicines to small groups of people via its recent measures around Rare Diseases. An important first step towards no longer neglecting Essential Medicines for Neglected Diseases is to explicitly identify them and situate them within the Canadian context. Undergoing the process of developing a Canadian Essential Medicines List with explicit reference to the World Health Organization Model List of Essential Medicines as well as national and international treatment guidelines is a valuable means of contextualizing drugs of global importance in Canada. The resulting classifications of drugs can then inform interventions in numerous areas, including high-profile domestic issues like the implementation of pharmacare, as well as help Canada meet its international obligations.

Once key drugs are identified, the question then becomes how to get them to the people who need them. Existing mechanisms like the Special Access Programme are insufficient to the task, even after recent reforms. Further improvement to mechanisms for accessing unapproved medicines are possible, and indeed may offer some benefits for access, but particularly in the case of Essential Medicines, are highly unlikely to prove as satisfactory as market entry. Essential Medicines are not second-class medicines, and the patients who need them should not be treated as second-class persons. For medicines internationally recognized as the standard of care, Canada needs to move beyond an ossified, dogmatic approach to regulation, particularly when the barrier to market entry is not any of the regulatory goals of safety, efficacy and quality, but the failure of the market itself. Here, acceptance of international standards such as WHO Prequalification

premised on the International Pharmacopoeia offers a promising path forward, with the Global Drug Facility offering an example of a role Canada can play within the international context. Essential Medicines offer a easy and logical initial foray into accepting international standards, one that can be further bolstered by active federal participation in areas like domestic procurement, and via lending Canada's support to building and maintaining the standards of WHO Prequalified drugs abroad. In turn, such actions not only directly benefit Canada, and the disproportionately vulnerable Canadians who require these drugs, but coincide with Canada's broader aspirations both for regulatory integration and for global health leadership. Essential Medicines for Neglected Diseases thus offer a useful prescription for reform that should not be neglected.

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