

What is the international landscape of essential medicine patent protection and how can
developing countries' medicine access be accelerated within it?

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Abstract

This project is at the controversial intersection of medicine patent protection and access to medicines at the international level. Advocates for medicine access argue that medicine patent protection may allow prices to become elevated, thereby frustrating medicine access. But advocates for medicine patent protection argue that the patent system incentivized the research and development to make the product possible in the first place. While this ideological debate is valuable, this doctoral project acknowledges the patent system's existence and seeks to produce research to advance medicine access pragmatically within this context, especially in developing countries and especially for drugs appearing on the World Health Organization's Model List of Essential Medicines (MLEM).

In cooperation with the World Intellectual Property Organization, this project commenced with a legal study to assess the patent status of the entire MLEM (375 medicines) in 137 developing countries. Gathering these patent data and verifying them with global pharmaceutical suppliers was this project's principal data collection. The patent data were further linked to development indicators of the countries implicated by our study and to economic data detailing medicine procurements made by those working with assistance from international organizations. Building upon the techniques refined during the MLEM study, three supplementary patent studies were performed to investigate very specific questions regarding medicine patenting and medicine access.

With these patent data collected, we investigated companies' medicine patent filing behaviours internationally. Various policy approaches to accelerating access at the international level were compared, including those that disregard patent protection and those are based on cooperation between medicine suppliers. Of the approaches considered, the cooperative approaches appeared to be the most efficient, especially voluntary licensing practices (i.e., originator companies license generic manufacturers to supply the product to

developing countries in exchange for royalties). We find that while patents may detour generic competition at times, we also find they may serve as springboards for collaborative endeavours and global medicine access campaigns, like the one for HIV drugs. This thesis concludes by arguing that improved international medicine patent transparency by pharmaceutical suppliers is one of the most powerful ways to foster such collaborations to improve medicine access.

Co-authorship

I am deeply grateful that this dissertation work was conducted within the context of regular mentorship, consultation, and input from a number of individuals, especially its supervisor Professor Amir Attaran.

After composing the Introduction and Conclusion chapters, feedback from internal committee members was collected and appropriately revised. I am thankful to Ronald Labonté, Doug Coyle, and Douglas Angus for serving on my internal committee while I was preparing this dissertation manuscript and reviewing for its defense. Additional input was gathered from the committee through the thesis defense process.

With respect to the composition of the articles contained in this thesis work, a collaborative approach was taken. The co-authors' contributions for each one is noted below. Each of the articles below has been peer-reviewed by an academic journal and has been revised accordingly.

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List of Acronyms and Abbreviations

ARV – Antiretroviral

CFC – Chlorofluorocarbon

CLs – Compulsory Licenses or Compulsory Licensing

COPD – Chronic Obstructive Pulmonary Disease

CVD - Cardiovascular disease

FDC - Fixed-dose combination

INPADOC - *IN*ternational *PA*tent *DOC*umentation database, which is maintained by the European Patent Office

GDI – Gross Domestic Income

GDP – Gross Domestic Product

GPRM – (World Health Organization’s) Global Price Reporting Mechanism

HDI – Human Development Index

HIV, HIV/AIDS – Human Immunodeficiency Virus infection / Acquired Immune Deficiency Syndrome

HFA – Hydrofluoroalkane

INPADOC – *IN*ternational *PA*tent *DOC*umentation

KEI – Knowledge Ecology International

LEM – (National) List of Essential Medicines

LDCs – Least Developed Countries

MPP – Medicines Patent Pool

MSF – Médecins Sans Frontières (Doctors without Borders)

MLEM – Model List of Essential Medicines

PEPFAR – (United States) President’s Emergency Plan for AIDS Relief

R&D – (Pharmaceutical) Research and Development

TNUs – Total Number of Units

TRIPS – Trade-Related Aspects of Intellectual Rights

USFDA – United States Food and Drug Administration

UNHLP – United Nations Secretary-General’s High-level Panel on Access to Medicines

VLs – Voluntary licenses or Voluntary Licensing

WHA – World Health Assembly

WHF – The World Heart Federation

WHO – World Health Organization

WIPO – World Intellectual Property Organization

WTO – World Trade Organization

Introduction

This dissertation work is a portfolio of six interrelated articles (Chapters 2-7), which are designed to be standalone manuscripts and address aspects of project's ultimate research questions. This Introduction section provides a broad overview of the project's main elements (i.e., its research question, objectives and goals, and methodological approach) and situates it within the field of population health and within the access to medicines literature, both in terms of theory and in terms of previous empirical studies in these areas. The Introduction ends with a summary of the dissertation's subsequent chapters and concluding section. Note that this introduction is largely a revised version of the original thesis proposal document, which was approved by its committee in May 2014.

1.1 Research question

This dissertation research is at the controversial intersection of medicine patent protection and access to medicines in developing countries. Advocates for medicine access argue that medicine patent protection may allow prices to become elevated beyond what is reasonable, thereby making medicine access suboptimal. But advocates for medicine patent protection argue that it is the existing system which brought these lifesaving products to reality in the first place (1). While this ideological debate is valuable, this project acknowledges the reality of the patent system as an integral component of how modern pharmaceutical research and development (R&D) is done and seeks to produce evidence-based research on how to pragmatically advance equitable medicine access within this context, especially in developing countries and especially for drugs appearing on the World Health Organization's (WHO) Model List of Essential Medicines (MLEM) (2).

Accordingly, this project's overall research question (and title) is as follows: "What is the international landscape of essential medicine patent protection and how can developing countries' medicine access be accelerated within it?" Note that the term

“landscape” here is used to broadly refer to the geographic coverage of medicine patents in developing countries; to the methodological exercise of mining patent databases in order to map such coverage in order to inform policy (i.e., patent landscaping); and finally, to the nature of those patent filings (e.g., what aspects of the novel product are and are not patent-protected) and of companies’ patterns in medicine patent filing behaviours internationally.

1.2 Objectives and goals

The objective of this research is to identify specifically where essential medicine access and medicine patent protection may come into conflict, and to identify which strategies have been effective at accelerating access to generic medicines within the context of patent protection in developing countries. The ultimate goal is to contribute to the acceleration of the diffusion of innovative medicines to developing countries and to reduce the inequitable disparity in essential medicine access that exists between rich and poor nations—a pursuit squarely within the agenda of population health, as defined by Kindig and Stoddart (3).

1.3 Theoretical background: Medicine access as a determinant of health inequities

1.3.1 Population health and the social determinants of health

At its core, the field of population health is concerned with how social inequities shape population-level health outcomes and health inequities (3-6). A large body of empirical evidence has been accumulating since the 1970s which demonstrates that socioeconomically disadvantaged populations have worse health outcomes (7-10). This heterogeneity has been documented between nations, within nations, and even applies to the world’s most highly developed and wealthy societies (4, 11-13).

Socioecological frameworks have been developed to conceptualize the fundamental causes of health inequities as being the unequal distribution of “flexible resources” (14) (wealth, power, knowledge, prestige, beneficial social connections, etc.) that shape

populations' differential capabilities to meet their everyday needs within a socio-economic and -political structural environment that further privileges some groups over others (14-20). These theoretical frameworks include upstream factors, such as education, living and working conditions, and food security, but also include downstream factors, such as differential access to quality healthcare products and services (21, 22). The WHO Commission on the Social Determinants of Health has developed a framework that depicts relationships between these determinants (4, 5). As is shown in Figure 1.9.1, the determinants of health interact across sectors and levels to shape inequalities in health outcomes.

While this research project focuses on the health system, it is critical to understand the greater system outside of it that shapes social and health inequities. There is much more to health and the prevention of disease than healthcare. The solution to social and health inequities is not a new pill, as enticing as such silver bullet interventions might be. Pharmacologic solutions cannot alter the unequal distribution of the aforementioned flexible resources across populations or the structural environment that they are distributed within. Social change in the upstream areas (the "causes of the causes" (23)), as well as the downstream areas, is required to realize the most substantial and sustainable gains in "leveling up" (21, 22) public health outcomes across populations (24).

1.3.2 The health system as one determinant of health and health inequities

Indeed, the overall project of population health as a field is acting upon multiple parts of the system simultaneously, intervening across sectors, and working towards equity in both the upstream and downstream determinants of health in order to trigger a more sustainable system-wide change (25-27). This includes the health system. As is shown in Figure 1.9.1, the upstream determinants channel downstream into the health system, and then feed back into the system upstream (4, 5). Health systems, therefore, are uniquely

situated to alleviate or reinforce the social inequities that feed into them by allowing for already advantaged populations to get priority access (4, 5, 28). Unfortunately, a cruel irony of our global society is that of the so-called “inverse care law”—i.e., the already healthiest populations have the best access to quality healthcare while the populations enduring the heaviest disease burdens have the worst access to healthcare (21, 29). This is phenomenon is especially pronounced at the international level (i.e., between countries), but is also observable within countries. Interventions targeting inequities in the health system, then, are crucial and should be one aspect of addressing population health inequities, but these alone cannot cause systemic change.

1.3.3 Medicines and medicine access as a component of health systems

The health system depicted in Figure 1.9.1 is itself a complex system (30). Health systems include the wide array of organizations, services, people, and products aimed at improving health outcomes. The WHO identifies six building blocks for strengthening healthcare systems and equity, one of which is medicines. They write: “A well-functioning health system ensures equitable access to essential medical products, vaccines and technologies of assured quality, safety, efficacy and cost-effectiveness, and their scientifically sound and cost-effective use” (31). Indeed, medicines (and access to those medicines) is a central component of most health systems today.

Regarding medicines more specifically, there are many activities related to their distribution and use (e.g., manufacturing, regulating, evaluating, prescribing, dispensing, and paying for them). Bigdeli et al (32) have suggested a conceptual framework for equitable medicine access, which attempts to encapsulate many of these factors. The authors name four critical inputs into the framework, one of which is “innovation: new medicines, formulations, and delivery channels” (32). Note that, for the purposes of developing this framework, these authors do not address the subject of what should qualify

as a useful and meaningful definition of “innovation” or whether the patent system may actually prevent innovation under certain circumstances (71), but rather have used a functional definition based on these experts’ observations of the real world workings of the health system. In other words, their definition is descriptive, rather than prescriptive.

The important point reflected in this framework for the purpose of this project is that pharmaceutical research and development (R&D) is one factor that can influence equitable medicines access. In other words, R&D is a determinant of equitable medicine access. The upshot is that equitable medicine access is not only a question of who gets access to which medicines and when, but also of which medicines get developed in the first place and for whom.

1.3.4 The patent system as a component of pharmaceutical R&D

The patent system has incentivized entrepreneurs to create new and useful products that benefit society for centuries. In exchange for disclosing technological knowledge and for building new industries, nation-states grant patents to innovators. Patents give the innovator the exclusive right to sell their invention in that country for a fixed period of time (usually 20 years). Should others enter that market prematurely, the patent gives the rights holder the prerogative take the infringer to court to seek compensation. The assurance of exclusive market rights can incentivize entrepreneurs with a compelling business case for invest substantial resources into bringing new products to market (33).

The pharmaceutical sector is no exception. In fact, patent system is such an integral component of the pharmaceutical R&D system that the WHO, the World Intellectual Property Organization (WIPO), and the World Trade Organization (WTO) have formed a trilateral commission to discuss the matter annually. Its most recent report uses the word “patent” 1,487 times in 257 pages (34). Corey Salsberg, Head International Intellectual

Property Policy at Novartis, called the patent system *the* major driver of pharmaceutical R&D in his testimony to the United Nations Secretary-General's High-level Panel (UNHLP) on Access to Medicines (35). Pharmaceutical manufacturers' associations and lobby groups (e.g., the Pharmaceutical Research and Manufacturers of America) argue that the patent system is "vital" to their business model (36). The current state of affairs is indeed that the industry perceives the patent system as a fundamental component of the modern pharmaceutical R&D system; the existence of this perception by the industry is not controversial. (37). Note, however, that whether the industry's loyalty to the patent system is based on convention rather than the empirical reality of what actually drives useful pharmaceutical innovation most effectively is another researchable and controversial line of inquiry, but is beyond the scope of this thesis.

1.3.5 Patents and equitable medicine access: The innovation and diffusion problems

The patent system's role in the pharmaceutical industry is one of the most debated topics in the access to medicines field (38). There is indeed good reason for caution about embedding the patent system within the pharmaceutical R&D. From a theoretical perspective, there are at least two important ways in which using the patent system to fund the creation of healthcare products may reinforce health inequities and the inverse care law; for brevity, the first is referred to here as the "innovation problem" and to the second as the "diffusion problem."

1.3.5.1 The innovation problem

The "innovation problem" has to do with which new drugs get developed in today's globalized world and for whom. Since the development of new medicines requires tremendous upfront investment, innovators necessarily target health problems that affect large populations with wealth so that they can recuperate their investment dollars and make a profit. Otherwise, it is difficult for commercial companies based in wealthy countries

to make a business case for investing. The issue is that there is not perfect overlap between the health needs of the world's wealthiest populations and its poorest ones (39). Therefore, new medical innovations are likely to disproportionately cater to the interests of already privileged groups with relatively better health, rather than those of vulnerable minority populations with relatively poor health.

The WHO has termed "Type III" diseases as those which predominately impact poor countries and for which the traditional pharmaceutical R&D models based on the patent system have largely failed to fund drug development (40). Neglected tropical diseases are examples of Type III diseases as they are unique to low-income countries and R&D dollars are rarely invested in creating vaccines or other medicines to treat them. Interventions targeting the innovation problem, therefore, typically involve supplementary or alternative funding models to the patent system for financing the development of pharmacologic solutions for Type III illnesses. The Drugs for Neglected Disease Initiative (DNDi) is an example of one such intervention (41).

1.3.5.2 The diffusion problem

In contrast to the innovation problem, the "diffusion problem" arises in contexts wherein new drugs have been developed for health problems that impact both rich and poor populations. The WHO has termed "Type II" diseases as those that are "incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries" (40). An example of a Type II disease is HIV/AIDS. While HIV/AIDS medicines were developed, tested, and priced for use in high-income countries, they have nevertheless been extremely effective in lower income countries in Africa that have been hit hardest by the epidemic. With exception to the development of formulations that would enhance access in developing countries (e.g., heat-stable formulations), the challenge here has typically been

more about getting these medicines to patients in low-income countries, rather than about getting them developed in the first place (34).

Similarly, the WHO has further termed “Type I” diseases as those that are “incident in both rich and poor countries, with large numbers of vulnerable populations in each” (40). An example of Type I diseases are non-communicable diseases, such as cardiovascular disease and cancers (42). The demographic profiles (and their corresponding epidemiologic profiles) of the world’s middle-income countries are looking increasingly similar to those of rich countries, meaning that these populations increasingly share many of the same disease burdens (43). Another contributing factor for this epidemiological convergence is likely the increasing level of trade between rich and poor nations. Disease has followed trade routes throughout human history (44). Studies have found positive associations between the increase of free-trade agreements in developing countries which facilitate increased consumption of tobacco, alcohol, sugar, and preserved foods, and an increase in related non-communicable diseases (45). Similar to the HIV/AIDS situation, new and promising pharmacologic solutions have been developed for wealthy populations that are expensive and patent-protected, but are also useful to lower income countries. Here again, with exception to the development of formulations that would enhance access in developing countries (e.g., cardiovascular polypill co-formulations), the challenge for Type I diseases is typically less about attracting more dollars for R&D and is more about disseminating those drugs with equity to the populations that need them most.

When the status quo is such that already advantaged populations systemically gain access to new health products before disadvantaged ones, it may contribute to reinforcing health differences between populations. In other words, the diffusion problem’s temporal component has to do with the differential dissemination of already existing medical innovations in a global commercial environment. Manufacturers will necessarily target the

largest markets first, i.e., large populations with wealth, before others in order to realize the biggest gains for their investors. Further, since patent protection confers market exclusivities, medicine prices may become elevated in the absence of competition and may be out of reach for smaller and/or resource-poor populations. This problem can become particularly pronounced at the international level.

Interventions addressing the diffusion problem for Type I and II diseases, therefore, seek to accelerate low-income countries' access to key pharmaceutical products. The diffusion problem is particularly distressing because these are scenarios in which lifesaving drugs already exist for patients, but they simply cannot yet access them for a variety of reasons (many of which have little to do with the patent system or medicine prices, such as poor delivery pipelines); the injustice of this state of affairs is particularly troubling and engenders a very high sense of immediacy and urgency. This has been the impetus for *ad hoc* global medicine access campaigns such as the one for HIV/AIDS medicines. It is also one reason for this project's emphasis on the diffusion problem.

1.3.5.3 The diffusion of innovations curve

There has been empirical and theoretical work done on the diffusion of new innovations, both inside of the health sector and outside of it. The first came from Rogers' in the 1960s. He observed that populations adopt new knowledge and innovations at differential rates, following a bell curve shaped pattern beginning with the "innovators" and "early adopters" and ending with the "late majority" and "laggards" (46). The field of health promotion has built upon this model to explain why the uptake of new health knowledge and innovations differs across groups, especially between those that differ socioeconomically (47). Victora et al (48) show powerful evidence of this pattern from cohort studies in Brazil. They show that public health interventions reached the highest socioeconomic groups (and improved health outcomes) before reaching those with lower

socioeconomic status (and improving their health outcomes), even though these interventions were intended to be delivered at an equal rate across the population. (Note that these authors also connect this diffusion problem as a contributing factor to the aforementioned inverse care law.) These differential diffusion patterns may apply to other new products, even those that are harmful to health. For example, empirical studies on the diffusion of smoking show that the practice was first adopted by upper-class men, then by upper-class women, then by lower-class men, and finally by lower-class women; the abandonment of smoking practices has followed the same pattern (21, 49).

The relevance of the diffusion of innovations model to this project is twofold. First, new knowledge and products (even unhealthy ones) are disseminated at differential rates—especially in commercial environments—regardless of the patent system, though the patent system may reinforce those patterns. Second, while one cannot realistically expect to change the shape of the diffusion of innovations curve, interventions can be designed to compress the diffusion curve by targeting access campaigns at the worst-off and hardest-to-reach groups. This is one of several approaches for tackling health inequities (50-52), which has been suggested by Benach et al (53).

1.3.6 Compressing the diffusion curve of essential medicines

In sum, there are many instances wherein existing medical innovation systems—of which the patent system is an integral part—have generated new pharmacologic interventions that are badly needed by developing countries (i.e., Type I and Type II diseases), but the diffusion problem remains and reinforces the inverse care law and the world's population health inequities. This project focuses predominately on these instances (i.e., Type I and Type II diseases), where medicine patents may contribute to that problem in the developing world, and what can be done at the international level given the reality of the existing system to accelerate access and compress the diffusion curve.

As for which medicines to focus upon, the WHO has developed the Model List of Essential Medicines (MLEM). The MLEM is a list of priority medicines that are known to be effective and that everyone should have access to, regardless of where they live or how much money they have; when it comes to access to medicines, the MLEM is the bare minimum starting point (2). Thus, the starting point of this population health project was to locate which products on the MLEM are patent-protected and undertake case studies to investigate their patent situation and how it may interfere with their dissemination.

1.4 Literature review: The WHO's MLEM, patent status, and medicine access

A literature review of the WHO's MLEM, patent status and medicine access has been published elsewhere (54), but is reproduced here with revisions and with permission.

When the WHO Expert Committee on the Selection and Use of Essential Medicines adds a new medicine to its MLEM, it encourages individual countries to add it to their own national List of Essential Medicines (LEM) and to internal medicine registries (55). Similarly, several foundations and non-governmental organizations base the medicines they supply to lower-income countries on the MLEM (56). The MLEM, therefore, has influence on the availability of medicines in lower-income countries. The WHO MLEM Expert Committee updates its work biannually, taking account of changing epidemiological profiles of developing countries and of the evidence base for new medicines that have come onto the market (57). Medicines are included irrespective of patent status and cost (though cost-effectiveness is a criterion for inclusion when two similar products are considered) (56).

As discussed in the previous section, there are many determinants of access to medicines; this includes medicines' prices (32). The WHO identifies "affordable prices" as one of four conditions in its "access to medicines framework" (58). As a patent owner may be an exclusive supplier in the market of a medicine covered by patent protection, prices could be raised beyond what is affordable for individuals or third-party payers, although

the prices of medicines depend on various factors other than patents, such as a national insurance schemes. The extent to which MLEM products are patent-protected in low- and middle-income countries is therefore an important consideration when addressing potential barriers impeding access to essential medicines (42).

Given the consensus on the global public health importance of MLEM products, many observers are often surprised to learn that there is no international medicine patent register and that it is not standard practice for global medicine suppliers to disclose their international patent holdings globally, not even for essential medicines. Nor has it been the practice of the international public health community to demand that companies disclose information on their medicine patent holdings globally. Consequently, aside from the legal professionals working within the intellectual property divisions of global medicine-supplying companies, the current international patent landscape for medicines is not clearly understood by global health actors and policymakers, not to mention the general public (59).

This lack of understanding introduces considerable unknowns into the debate regarding the potential conflict between access to medicines and patents in developing countries. In the absence of sound data, the debate quickly becomes polarized. Furthermore, when information around essential medicine patents is opaque and inaccurate, it may discourage or unnecessarily alter the actions of importers, exporters, generic manufacturers and other global health actors who fear infringing upon intellectual property rights (e.g., unnecessarily buying originator over generic) (60, 61). Given the WHO's prioritization of the medicines on the MLEM, it follows that the patent status of these medicines should be transparent to those who buy medicines, both to maximize value for money and to avoid patent infringement (62, 63).

The international patent status of essential medicines became a key concern particularly as the list grew to include several new and patent-protected antiretrovirals for treating HIV/AIDS in 2002 (56). Shortly thereafter, Attaran conducted the first academic assessment of the patent landscape for the entire MLEM, which was published in 2004 (64). This study brought empirical clarity to the debate on whether patents were interfering with access to essential medicines in developing countries. It demonstrated that only six percent (19 of 319) of medicines appearing on the 2003 MLEM were patent-protected (most were HIV medicines) and that such patent protection did not extend into many developing countries, since many companies never filed patent applications there.

Attaran's study brought to light the importance of understanding the essential medicine patent landscape. Simply put, it is only where patents for a given medicine exist, either locally (i.e., in the consumer's country) or in the manufacturer's country (i.e., in the exporter's country), that patents can lawfully impede access. Knowing where patents exist (and do not exist) helps remedy such misunderstandings and frustrations. It also paves the way for cooperation between global health actors, regardless of their ideological leanings, because it can identify the problem areas where they can work together to mitigate any medicine access issues in developing countries that have resulted from patent protection.

Since the MLEM is updated biannually, it is important to keep current the understanding of the essential medicine patent landscape. The WIPO and the WHO approached Cavicchi and Kowalski at the International Technology Transfer Institute of the Franklin Pierce Center for Intellectual Property at the University of New Hampshire School of Law to conduct a similar patent landscaping exercise for the 2009 and 2011 updates of the MLEM (65, 66). The current project—especially with respect to Chapters 2-4 (Articles 1-3)—continues in this tradition using the 2013 MLEM, building upon the data and methods of the previous reports. It was commissioned by WIPO's Global Health Challenges Division

in 2014. At the request of WIPO, the patent survey was enlarged from that of previous studies to include all low- and middle-income countries (137 countries in total), making it the largest MLEM patent study to date.

The WIPO report (54) and its companion policy brief (67) were published on 12 April 2016, which were launched at a Global Challenges Seminar in Geneva (68). The purpose of these two publications was primarily to provide the MLEM data located by this project, fully describe the methods used to collect those data, and provide basic descriptive statistics about the dataset. As was previously agreed upon with WIPO, however, more sophisticated analyses of the data were reserved for separate journal articles, which were to be published as standalone pieces. These standalone articles are Chapters 2-4 (Articles 1-3) of this dissertation. Chapters 5-7 (Articles 4-6) are extensions of the same patent search, data mining and linkage techniques, but use different datasets to explore other aspects of medicine patent protection as a potential access and development barrier.

1.5 Methodological approach

The methodological design that ultimately binds the chapters of this dissertation project together is that of multiple comparative case studies embedded within one single larger case study, as has been described by Yin (69). This project's overall unit of analysis is the MLEM. The MLEM forms the backdrop context for the individual cases of this project. The individual cases are those MLEM drugs that could be considered patent-protected and were identified by mining patent and medical product databases. Our findings were validated by supplier companies (see the WIPO report for the methods by which this was done (54)). Each patent-protected MLEM drug represents an individual case, which is embedded within its own unique context (e.g., target disease, drug maker(s), etc.) has its own patent estate (i.e., the list of patents that have been filed for the product in developing countries internationally).

In order to learn more about each case and about the collective set of cases, the patent data were linked to secondary sources on the countries into which companies had filed essential medicine patents (Chapter 3/Article 2), to international procurement data available on the HIV medicines (Chapters 4-5/Articles 3-4), and to licensing agreements between patent-holding companies and generic suppliers (Chapter 4/Article 3). Multiple methods of analysis for this interdisciplinary project were then used to better understand “the case”, i.e., its landscape, and its potential to impact medicine access. The analytic methods were adapted from a variety of fields and approaches, including those of systematic reviews and meta-analyses, epidemiology, pharmacoeconomics, law, statistics, and policy analysis. Each chapter within this thesis contains its own methods and analysis section, and provides necessary detail for each component.

To be clear, Chapters 5-7 (Articles 4-6) are extensions of the same patent search and data mining and linkage techniques, but these chapters are based on datasets that were compiled specifically for those projects, rather than upon those from the WIPO patent study on the MLEM. These data sources and methods are detailed in each article. These additional undertakings served to apply principles derived through the WIPO project (Chapters 2-4) to other questions about patent protection as a potential access barrier to existing and future essential medicines. Indeed, another methodological feature that binds together this dissertation’s articles (Chapters 2-7) is the common use of patent data mining and data linkage techniques. These additional articles (Chapters 5-7) served to increase understanding of the overall case, i.e., the MLEM and the patents that it implicates globally, and how these may (or may not) impact medicine access in developing countries.

1.6 Ethical considerations

The principle data collection for this project is pharmaceutical patent data, which are part of public record. All other data that were used to link to the patent data, such as

pharmaceutical procurement data, are secondary data that are available to the public online. The exact data sources are discussed in the methods section of each article. Given that this project's data were to be derived by mining secondary sources, the thesis proposal committee agreed that a formal ethics approval was not required unless a key informant interview of the project was pursued, which was originally proposed as the final component at the conclusion of the study. The key informant interview component of this project, however, was *not* pursued. This was in part due to the fruitfulness of the data linkage and its relevance to informing policy recommendations, concerns of thesis proposal committee members about key informant selection given the number of case studies, and feasibility challenges given the available resources and timeline to complete the project on schedule.

1.7 Overview of the dissertation

This dissertation is a portfolio of six interrelated articles in which the candidate was the lead author. Each chapter has been written to be a standalone manuscript that addresses the theme of project's ultimate research question (and title). Similar to an edited book and in contrast to the traditional dissertation in the form of a single monograph, its chapters have been written by different sets of co-authors and can be read independently of one another and in any order. Each article has been peer-reviewed and has either been published by a reputable journal during the course of study or will soon be published. An "Authors note" page at the beginning of each article lists the co-authors and affiliations as well as the publication information where relevant. Consistent with the typical format of scientific articles, each chapter includes its own introduction with a brief literature review, a description of the methods, summary of the results, and a discussion of the study's implications and conclusions.

1.7.1 Chapter 2 (Article 1) - Which patent and where? Why international patent transparency is needed for medicines

Chapter 2 (Article 1) takes critical pause to look at the objective of the WIPO study and understand why determining a medicine's patent status is so difficult in the first place. To investigate this question, we compared our international patent search results derived by using the most common technique employed by third parties to evaluate medicines' patent status (which we call the "linkage method") against companies' records. We found that while the linkage method can be reasonably accurate, it is not consistently or predictably so. This result lays a logical and empirical basis for demanding from multinational pharmaceutical companies that they practice of international patent transparency. Given the importance of patent information to medicine procurement and policymaking activities, this chapter suggests that international patent transparency itself is an intervention that could accelerate access in developing countries (70).

1.7.2 Chapter 3 (Article 2) - In which developing countries are patents on essential medicines being filed?

Chapter 3 (Article 2) describes results of the main data collection performed while working with WIPO. It focuses on answering the basic question of where MLEM patents are typically filed. We find that simply a country's population size is the most predictive variable with associations that were even stronger than economic ones that previous studies had already identified as significant. We find that just a few essential medicine patents placed in a few medicine-exporting countries (e.g., India) from which most low income countries import their medicine supplies and where a substantial proportion of the developing world resides, medicine patenting does have large potential to influence access to some key essential medicines. Therefore, approximating the potential impact of patents upon access to these medicines based only on the number of patents and the countries

covered by them—without taking into account population size and medicine exporting activities—could result in significant underestimations (71).

1.7.3 Chapter 4 (Article 3) – Accelerating access to generic HIV medicines in developing countries that have granted patent protection

Chapter 4 (Article 3) takes aim at answering the question of the extent to which generic competition can exist within the context of patent protection. It links the patent data collected during the WIPO patent study to corresponding HIV procurement data. It finds that—at least within the context of the global campaign for HIV access—generic competition is actually more prevalent where there are patents than where there are none whatsoever (which corroborates the findings of Chapter 3/Article 2). Chapter 4 (Article 3) further links the procurement data to voluntary licensing agreement data between patent-holding companies and generic suppliers. It demonstrates that voluntary licensing is potentially one of the most often used mechanisms to facilitate access to generic HIV products where patent protection is in force (72).

1.7.4 Chapter 5 (Article 4) – Compulsory licensing often did not produce lower prices for antiretrovirals compared to international procurement

Chapter 5 (Article 4) investigates the effectiveness of compulsory licensing at reducing medicine prices (i.e., when a nation-state allows for the temporary use of a patented technology by third parties without the permission of the patent holder) as compared to other cooperative strategies, such as voluntary licensing. Chapter 4 (Article 3) found that compulsory licenses were seldom used relative to voluntary licensing; however, the literature has nevertheless focused far more upon compulsory licenses. This raised the question of whether compulsory licenses were more effective at achieving lower prices. We find that while there were indeed cases where compulsory licenses did derive the best

price, it was more often the case that cooperative strategies produced comparable or even better prices than compulsory licensing tactics (73).

1.7.5 Chapter 6 (Article 5) – Could patents interfere with the development of a cardiovascular polypill?

Chapter 6 (Article 5) focuses on a product which is not yet on the MLEM, and in fact does not yet exist, but has nevertheless been identified by the WHO as a priority—namely, a cardiovascular polypill. The polypill would contain several cardiovascular medicines commonly taken separately into a single pill in order to improve access, adherence, and clinical outcomes. While the polypill has been much discussed for over 15 years, no such thing is commonly available on the international market today. This chapter investigates the question of whether patent protection is a potential barrier. This study was done at the request of the World Heart Federation (WHF). It reports on the international patent status of 48 cardiovascular medicines. Based on the findings of Chapters 2-5 (Articles 1-4), it suggests that patents may represent springboards for access campaigns as much as they can represent barriers. It recommends two ways forward—each based on patents’ potential to block or to facilitate drug development—for the WHF to pursue the development of a cardiovascular polypill with drug-makers (74).

1.7.6 Chapter 7 (Article 6)– Is Patent “Evergreening” Restricting Access to Medicine/Device Combination Products?

Chapter 7 (Article 6) also addresses another important future trend in pharmaceutical patenting given the rise of non-communicable diseases globally, namely, patents on device-medicine combinations, such as inhalers and pens. These are key delivery systems for treating conditions such as chronic obstructive pulmonary disease and diabetes. While we found in Chapter 3 (Article 2) that MLEM products are often post-patent, we also found in Chapter 6 (Article 5) that drug developers continually redevelop drugs to maintain

their market edge through the creation of new formulations and co-formulations long after the expiration of the original active ingredient patent. This practice is known as “secondary” patenting and pejoratively as “evergreening”. Chapter 7 (Article 6) documents a lesser-known, tertiary form of this practice, namely, patenting on delivery devices. Tertiary patenting can continue long after all of the secondary patents on new formulations and co-formulations have expired. After demonstrating the widespread prevalence of this practice in device-intensive routes of administration, Chapter 7 (Article 6) then questions how to safeguard the health system from paying more for products for which patent has been granted, but which may not necessarily have a direct therapeutic benefit (e.g., designer insulin pens) (75).

1.7.8 Chapter 8 – Conclusion

This dissertation’s Conclusion is Chapter 8. It focuses upon this work’s most fundamental policy-relevant conclusion, namely, the importance of the practice of international medicine patent transparency by multinational pharmaceutical companies and the need for the eventual establishment of an international medicines patent register. It discusses actions that were taken during the study period to advance this cause, which included oral presentations to the trilateral symposium of the WHO, the WTO, and WIPO; to the UNHLP; and to a large group of stakeholders (primarily international organizations and non-governmental organizations) gathered by WIPO in Geneva. Part of the conclusion is also devoted to reflecting upon next steps in the research program and upon what has been learned through the experiences of carrying out this project about population health and about access to medicines.

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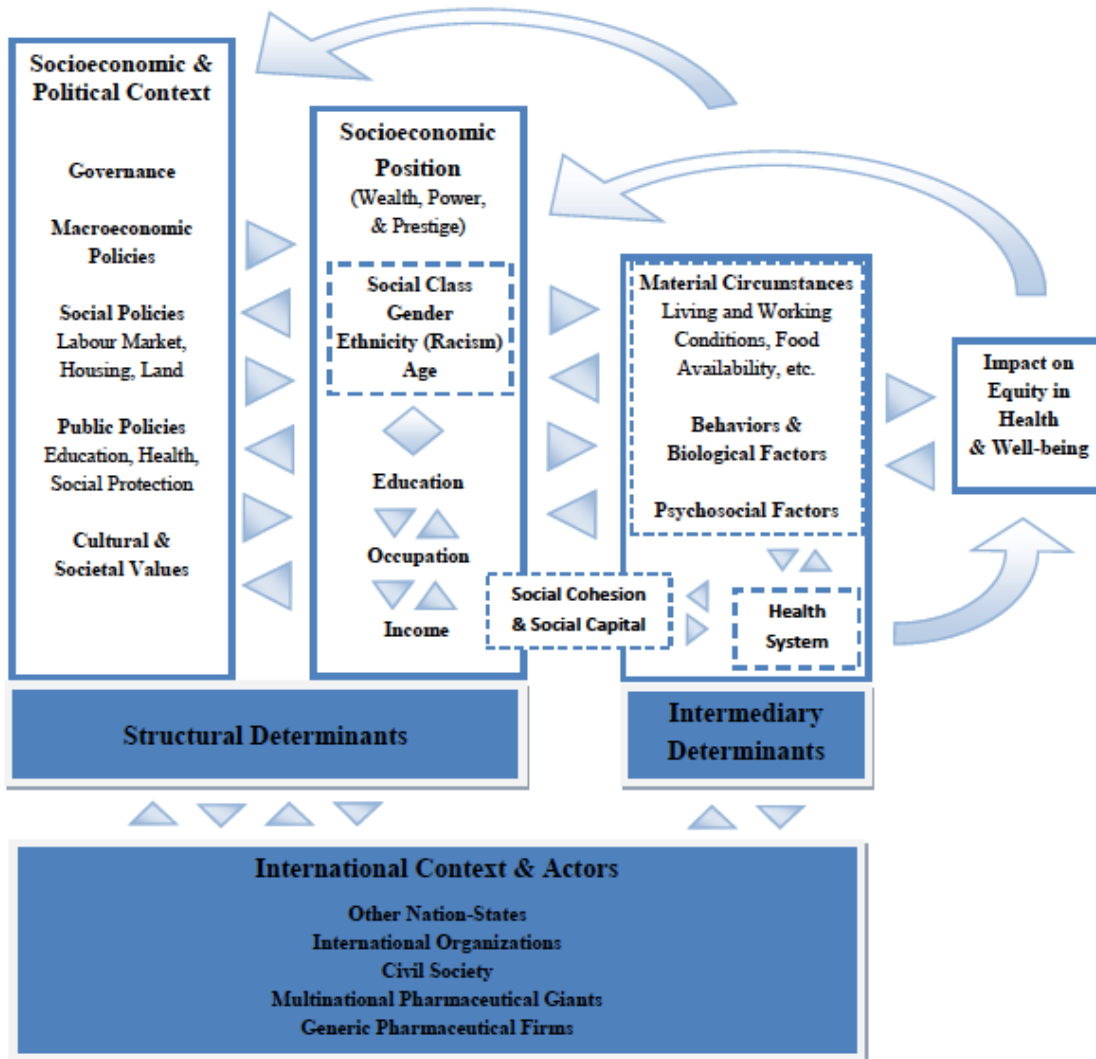
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1.9 Figures

Figure 1.9.1 Adapted framework of the determinants of health and health inequalities (4, 5)



Chapter 2 (Article 1):
Which Patent and Where?
Why International Patent Transparency is Needed for Medicines

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2.1 Abstract

2.1.1 Introduction

In the absence of an international medicine patent register, a common method for determining the patent status of medicines internationally is to use the patent information available in the American and Canadian national medicine patent registers to retrieve data on related ones abroad through international patent databases (e.g., INPADOC or Derwent) that group related patents globally (called the “linkage methodology” here). This approach has never been formally evaluated against company records. This study provides such an assessment.

2.1.2 Methods and materials

A preliminary list of patents internationally was produced using the linkage methodology for a sample of 16 medicines from the World Health Organization’s Model List of Essential Medicines. These were sent to global suppliers for validation and correction. Results before and after the validation exercise were then compared.

2.1.3 Results

The linkage methodology was 83 percent accurate collectively (i.e., across all 16 medicines) at the basic task of identifying into which countries global suppliers had been filing patents on these essential medicines. Only 70 percent of the positive results were correct; 30 percent showed patent protection in developing countries where there was none. There was wide variability when considering the medicines individually, with accuracy as low as 46 percent. A more detailed test comparing the patent numbers and expiration dates against company records showed that only 42 percent were correct.

2.1.4 Conclusion

Determining medicines’ patent status internationally with high accuracy and certainty is exceedingly difficult as a third party. Only supplier companies possess the best

information on which of their products are patented and where. Yet policymakers proceed without insisting on a complete and accurate picture of the global medicine patent landscape. We encourage suppliers to practice international patent transparency, for other stakeholders to demand it, and for these data to be stored in an international medicine patent register.

2.2 Introduction

There is no international medicine patent register, not even for products appearing on the World Health Organization's (WHO) Model List of Essential Medicines (MLEM) (1, 2). The inaccessibility of international medicine patent information has complicated global medicine access interventions for decades, most notably during the campaign for HIV medicine access in resource-poor settings (3, 4). International actors coordinating medicine procurement need patent information to optimize their purchasing choices on a fixed budget while still recognizing the varying levels of patent protections that may (or may not) be in force across countries at a given time (2). When patent status information is ambiguous or incorrect, it may unnecessarily mislead or delay the actions of importers, exporters, manufacturers, and other global health actors who may mistakenly believe that there is patent protection where there is none (1, 4, 5).

The most common method for determining a medicine's patent status internationally is (i) to consult the national medicine patent registers of the United States Food and Drug Administration's (USFDA) Orange Book (6) and/or Health Canada's Patent Register (7), and then (ii) to use these data to retrieve related filings in other countries through international patent databases (1, 5, 8-12). This is possible because international patent databases, such as the European Patent Office's INPADOC (13), group related patents globally into so-called "families" (14). Many published studies and methodologies (1, 5, 8-12) begin with this two-step approach to produce a preliminary "patent estate" report for a given product (i.e., a list of patent filings globally); we refer to this as the "linkage methodology."

While the linkage methodology is relatively quick and simple, there are several well-recognized limitations that may impact its accuracy, such as unlisted patents in the Orange Book or Health Canada databases, errors in how related patents are grouped, and

inadequate coverage of some developing countries by international patent databases like INPADOC. The accuracy of the linkage methodology, therefore, is unknown. Prior to our initial assessment (1, 2), the linkage methodology's accuracy has never been formally evaluated to the authors' knowledge. As supplier companies are in the position of acquiring patent rights, and maintaining and enforcing those rights, we consider their records to be the best available source. The objective of this study is to provide an assessment of the accuracy of the linkage methodology when compared to supplier company records.

2.3 Methods and materials

A recent study conducted in cooperation with the World Intellectual Property Organization (WIPO) of the 2013 WHO MLEM evaluated the patent status of 375 products in 137 developing countries (1, 2). As is detailed in the WIPO study, 20 drugs were identified as likely to be under patent protection in some developing countries. We compiled a patent estate report for each one using the linkage methodology. INPADOC (13) and Derwent (15) (accessed through the Thomson Innovation platform (16)) served as the international patent databases. Each list was sent to the respective supplier companies for verification and correction where necessary (e.g., patent numbers and expiration dates corrected, omitted patents added and irrelevant ones removed). The final step was to compare the patent estate lists before and after the companies' corrections. We were able to complete this procedure for 16 of the drugs.

The agreement between the pre- and post-verified patent estate reports was examined first in very basic terms and then in more detailed terms. For the basic test, the investigation of the concordance of a test dataset (i.e., the linkage methodology data) against a reference dataset (i.e., company records) was considered methodologically analogous to evaluating a screening or diagnostic test in public health epidemiology (17). We evaluated the linkage methodology's ability to correctly identify the mere existence of

one or more relevant patent filings across products and in the developing countries covered by INPADOC and Derwent; i.e., we tested how effectively it could provide a correct answer to the binary (yes/no) question of whether any patent records whatsoever were active (i.e., a live application or patent grant) in a given developing country for a given product. For the analysis, we borrowed techniques from diagnostic test accuracy reviews and meta-analyses and report our results accordingly. We used Review Manager 5 software by the Cochrane Collaboration to create Figures 2.8.1 and 2.8.2 (18).

For the fine-grained test, we focused on the true positive results (i.e., the individual cases in which the linkage methodology had correctly identified a patent filing in a particular developing country). We investigated the extent to which the patent filing record number(s) and/or expiration date(s) matched on these details in companies' records for the given country and tallied the results.

2.4 Results

Figure 2.8.1 lists our sample of 16 essential medicines included in this concordance study, along with the treatment categories, participating supplier companies, and information on exclusions.

Figure 2.8.1 also displays the results of the binary test, i.e., whether the linkage methodology provided a correct positive or negative answer to the question of whether any patent filings were active in a given developing country for a given product. With the results pooled across the 16 medicines and 137 countries such that products with more patents weight more heavily, the linkage methodology was correct on 83 percent (1060/1280) of the patent-product-country combinations and was incorrect on 17 percent (220/1280). Its sensitivity was 0.76 (i.e., it detected 76 percent of the positives) and its specificity was 0.86 (i.e., it located 86 percent of the negatives). Importantly, we observed that the predictive value positive was only 0.70 (299/299+126), meaning 30 percent of the positive results

were wrong. The predictive value negative was stronger at 0.89 (761/761+94), meaning that 11 percent of the negative results were wrong. In this test overall, the linkage methodology detected 519 essential medicine / active patent / developing country combinations while company records only showed 393; the coverage of essential medicines patents appeared to be 24 percent larger (126/519) in the developing world than it actually was. The linkage methodology is more prone to overestimate patent protection in developing countries than underestimate it.

When we considered results for each of the 16 medicines individually, there was wide variability in the linkage methodology's accuracy by drug. Many confidence intervals do not even overlap. The percent of correct results was as low as 46 percent (37/80) for didanosine, 54 percent (43/80) for saquinavir, and 56 percent (45/80) for pegylated interferon 2a. This variability was observable in other indicators as well, with sensitivity ranges from 0.27 to 1.00 (median = 0.76) and specificity ranges from 0.44 to 1.00 (median = 0.95).

Figure 2.8.2 illustrates ROC plots for the same test, which show the sensitivities plotted against the specificities. Strong tests tend toward the reader's upper left corner; worthless tests tend toward the dotted diagonal line. Panel 1 shows the disaggregated results for each product with the black circles and curve vis-à-vis the red diamond and curve for the pooled results. The pooled results show the linkage methodology has fair accuracy, with a more reliable specificity than sensitivity.

However, the disaggregated results show high variability by drug. Four results (all Gilead products) show very high sensitivity and specificity; four others had very poor sensitivity or specificity. There is no consistent clustering, reflecting the linkage methodology's low precision. Panel 2 in 3.8.2 further illustrates this imprecision, both between the databases (only three results were identical) and within the databases (an

absence of a single, clear cluster by either database). The results by product from both databases showed instances of very poor sensitivity, but generally good specificity with a few exceptions. The error by product, unfortunately, seems random, unpredictable, and does not have an obvious direction or bias. It appears that although the linkage methodology may have fair accuracy overall, it has low precision and is prone to reproducibility error.

2.4.1 Patent number, count, and expiration date accuracy

Confining our investigation to the true positive results exclusively, we checked whether the patent numbers and expiration dates derived through the linkage methodology matched any of those listed in the validated dataset for a given country and product. 41 percent of the patent numbers did not match one in company records for the product and country concerned. 44 percent of the expiration dates were incorrect; and of those, 23 percent were more than a year off. Only 46 percent matched on both publication number and expiration date.

We again observed wide variability in the accuracy of the linkage methodology's results across products. Across the 16 medicines, the median proportion that matched the company records on the patent number was 60 percent, with some as low as 15 percent (bevacizumab), 25 percent (omeprazole), and 31 percent (abacavir), but others as high as 100 percent (tenofovir, tenofovir+emtricitabine).

2.5 Discussion

Our study demonstrates the difficulty in determining a medicine's patent status globally as a third party. While medicine patent information is public, it is also inaccessible at the international level. Our study uses premium, commercial-grade databases, and even with these resources in our hands (which have considerable experience performing such searches), the linkage methodology's results show imprecision and imperfect accuracy.

Supplier companies hold exclusive access to the most correct and up-to-date records on products' international patent estates. We discuss here briefly implications for research and policy.

An implication for research is that the linkage methodology has utility as a starting point for gathering certain basic information, such as the supplier company and the patent owners. With a large sample of medicines, it can also provide estimations of global patent-filing trends. But it alone should not be relied upon when exactness or fine-grained analyses are required, such as determining a single medicine's patent status in a particular developing country, the type protection that has been afforded there, or when it will expire.

With respect to implications for policy, our finding that the linkage methodology is more likely to overestimate patent protection than underestimate it is noteworthy. One insight gained through this exercise on why this occurs is that companies seem to be routinely filing many very similar patent applications for each innovative feature of their medicines in order to maximize their chances of acquiring grants, especially in countries with relatively more market and manufacturing prospects (such as Brazil, China, India, Mexico, Philippines, and South Africa). Companies later shed redundant applications or non-viable applications (i.e., innovations that companies later decided to not pursue for whatever reason) by abandoning them or by allowing granted patents to lapse by neglecting to pay the maintenance fees. Another reason for this phenomenon is that companies file patents early in product's development prior to knowing which innovations are viable for the marketplace. Companies, therefore, file patent applications for each potential area of development and can later shed those if they decide against bringing the associated products to market. While both of these filing strategies are sensible, they greatly increase the number of dead patent records contained in international patent databases. This further complicates the task of distinguishing live patent records from dead ones, relevant patent

records from irrelevant ones. Legal status (i.e., whether the patent has been granted, is under review, etc.) on these records is not real time, is patchy and is often outdated. Consequently, patent records appear in international databases for countries where there are no unexpired patents whatsoever for the drug question.

This overestimation has consequences for international medicine procurement activities. To illustrate this, we cross-referenced our patent data with procurement data from the WHO's Global Price Reporting Mechanism (GPRM) (19) for the same products during the same time period as our patent study (20). The GPRM contained data on 156 million units of originator HIV medicine purchases relevant to our sample; according to our validated patent dataset, there was no relevant patent protection in the purchasing country for 84 percent (131 million units) of these procurements. We confirmed in the GPRM data that generic equivalents had indeed been procured elsewhere for 99 percent of these originator products. Therefore, the more expensive originator procurements were not motivated by the actual presence of patents or by a lack of availability of generic alternatives on the international market.

Why, then, were more expensive brand name products bought when less expensive ones were available? Certainly there may have been quality or supply consistency concerns, requirements by funders to buy brand name products, or other valid reasons. Nevertheless, a recent qualitative study commissioned by the WHO found that key informants working on public medicine procurement had significant trouble determining products' patent status in developing countries and tended to err on the side of caution, buying originator products rather than generics (4). In this way, uncertainty about a medicine's patent status could work favorably for originator companies and could be one driver towards patent non-transparency. Indeed, the fear that a product is patented can be as effective as it actually being patented.

But non-transparency can also work against originator companies and public health. Skeptics of the patent system relying on international patent databases are likely to misestimate companies' actual international patent holdings in developing countries, erring towards overestimation. Decision-makers may misdirect policy attention and are unable to focus on exact instances where intervention is necessary. Further, this opaqueness causes stakeholders to divide themselves along ideological lines and remain there, with advocates for access to medicines on one side and those for patent protection on the other. While the reasons behind these adversarial clashes go well beyond the patent issue, the lack of sound patent data aggravates matters by preventing researchers from finding empirical answers to fundamental questions regarding medicine access where patents have been granted in the developing world. Until data are made available, these stalemates will continue to repeat themselves.

Perhaps this phenomenon partly motivated GlaxoSmithKline to recently announce that it would join Merck KGaA in voluntarily "mak[ing] information about its patent portfolio freely available" (21). Novo Nordisk has disclosed its entire global patent holdings on its products' active ingredients (22). Patent transparency was raised at the most recent trilateral meeting of the WHO, WIPO, and the WTO (23, 24), and it is included as a component of the Access to Medicines Index (25). At least six other companies have disclosed their patent estates on select products to the Medicines Patent Pool (MPP) (26), which makes this information available on its website (27). Plus, after some persistence, most companies eventually participated in our study that were asked. Only Cipla refused repeatedly (1, 2). So, there is some encouraging willingness on the part of industry. And it stands to good reason that those benefiting from and advancing the medicine patent system should voluntarily do their part to be transparent about exactly where essential medicine

access and patent protection might come into conflict and to proactively address such instances.

Transparency is a powerful accountability tool, and it motivates action on licensing agreements to advance medicine access. It is no coincidence that GlaxoSmithKline's recent announcement about disclosing international patent information was paired with a declaration of its intent to expand its voluntarily licensing activities to generic manufacturers (21). From our experience, companies using the MPPs multilateral licensing system show particular comfort discussing their patent holdings for those products. Indeed, the best way for companies to prevent compulsory licensing is to offer their competitors voluntary licenses and/or offer the best value.

To be clear and prevent other similar misunderstandings (28, 29), the recommendation that follows from this study is that *companies* need to practice international patent transparency on medicines. The sheer volume of third-party patent studies illustrates this point. The most immediate solution at the international level is for companies to do so voluntarily. While patent studies by third parties have played (and will continue to play) a valuable role in understanding the global medicine patent landscape, these efforts cannot replace the need for companies to take action to make such transparency their industry standard. We would consider such disclosure to be a true show of transparency.

But the optimal solution remains to be an international medicine patent register, which would bring greater accountability to ensure medicine accessibility and patent quality. The need to establish user-friendly global medicine patent databases was resolved at the World Health Assembly in 2008 with a target deadline of 2015 (WHA61.21, 5.1c) (11, 30). That deadline has now passed, and there is still nowhere that one can simply enter the name of a drug and retrieve a complete list of all patents that companies are enforcing

internationally. Such a register could be driven by a consensus on the principle of no enforcement without disclosure in the database (4, 31). This aligns with the fundamental legal principle underpinning the patent system, namely, the disclosure of novel information in exchange for the option to enforce exclusive market rights (32). Further, this resembles the logic of other registers. For example, in order to benefit from the international system that has been set up for countries to export generic medicines via compulsory licensing (i.e., the Paragraph 6 System), the parties must enter this information into an international register maintained by the WTO (33).

The data ideally contained in an international medicine patent register would be organized by patent family and include the application and/or patent numbers, expiration dates, current legal status, and the type of protection covered (compound, formulation, co-formulation, manufacturing process, or method of treatment). Participation is also needed from generic companies, which hold patents on many co-formulations for HIV, and universities. This would preferably be paired with a place for companies to showcase their efforts to ensure affordable and sustainable access in developing countries where they hold patents, such as licensing agreements or proclamations to refrain from enforcing those patents. The register could, for example, be hosted by the Medicines Patent Pool; by WIPO, the WHO, and/or the WTO; or by another organization.

2.6 Conclusion

Determining medicines' patent status internationally with a reasonable level of speed, accuracy, and precision is exceedingly difficult as a third party. While the linkage methodology is useful for some patent search tasks, it is no proxy for a global medicine patent register, which would simultaneously foster a higher level of accountability to ensure medicine access and patent quality. The opportunity cost to public health for maintaining status quo is enormous. But companies can take immediate action by practicing

international medicine patent transparency. Other stakeholders should demand it from them. Given the significance of the debate on access to medicines vis-à-vis patent protection, policymakers should be insistent upon something extremely basic: to be given a correct picture of the current global medicine patent landscape. It should be on the World Health Assembly's agenda. Decisions based on inaccurate or outdated information are rarely optimal. We hope the High-level Panel on Access to Medicines recently convened by the United Nation Secretary-General's (UNHLP) (34) will demand transparency. As the global demographic and epidemiological transitions are likely to bring more patented medicines for non-communicable diseases like cancers to the MLEM, international medicine patent transparency has never been so important.

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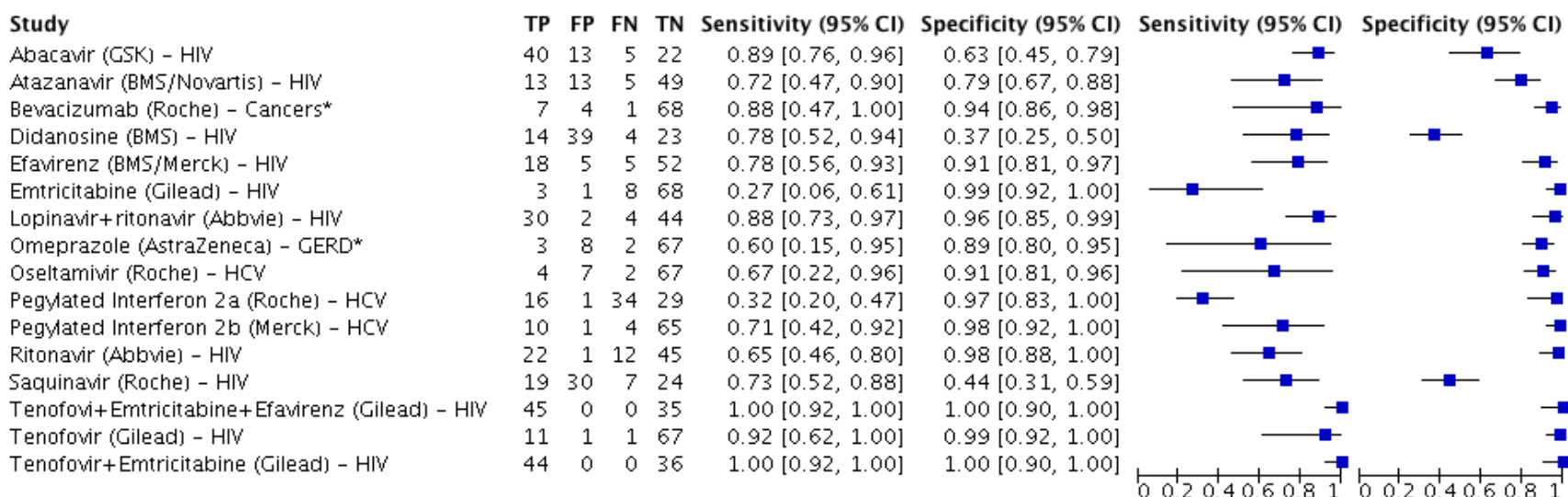
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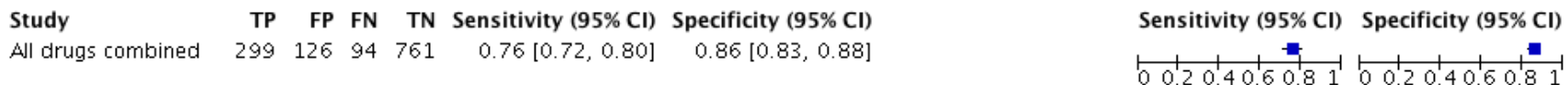
2.8 Figures

Figure 2.8.1 - Linkage methodology's identification of patent presence across products and countries compared to supplier companies' records

Linkage method - INPADOC + Derwent (products disaggregated)

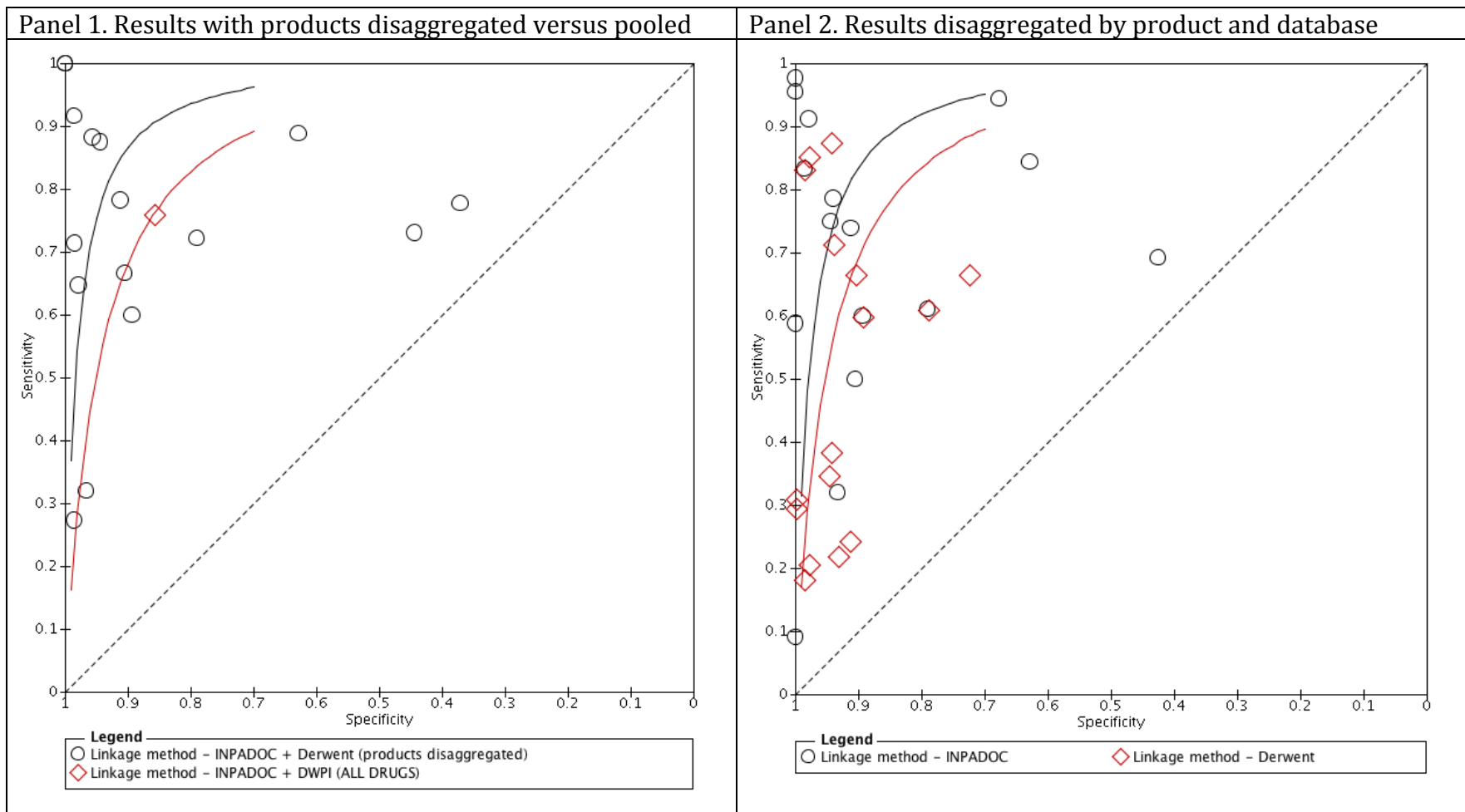


Linkage method - INPADOC + DWPI (ALL DRUGS)



* Bevacizumab is used for anti-vascular endothelial growth factor (VEGF) preparations to treat cancers of the colon, lung, kidney, cervix, ovaries, brain, and others. "GERD" is Gastroesophageal reflux disease. Four of the 20 drugs were not eligible for inclusion in this concordance study because (i) it was not possible to create a patent estate report in developing countries using the linkage methodology because the products were not listed in the Orange Book (lamivudine + nevirapine + stavudine, lamivudine + nevirapine + zidovudine) or because Orange Book patent family listed was expired (artemether + lumefantrine), and/or because (ii) the suppliers were unwilling to validate patent estate reports that were sent to them (InSite Vision's formulation azithromycin for ophthalmic preparations, and Cipla's lamivudine + nevirapine + stavudine for HIV). TP=true positive, FP=false positive, FN=false negative, and TN=true negative.

Figure 2.8.2 - ROC plot tests of the linkage methodology's accuracy with products disaggregated in INPADOC and Derwent



Chapter 3 (Article 2):

In which developing countries are patents on essential medicines being filed?

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3.1 Abstract

3.1.1 Background

This article is based upon data gathered during a study commissioned by the World Intellectual Property Organization on the patent status of products appearing on the World Health Organization's 2013 Model List of Essential Medicines (MLEM). It is a statistical analysis aimed at answering the following research question: in which developing countries are patents on essential medicines being filed?

3.1.2 Methods

Patent data were collected by linking those listed in the United States and Canada's medicine patent registers to corresponding patents in developing countries using two commercial-grade international patent databases (INPADOC and Derwent via Thomson Innovation). The respective supplier companies were then contacted to correct and verify our data. We next tallied the number of MLEM patents per developing country. Spearman correlations were done to assess bivariate relationships between variables, and a multivariate regression model was developed to explain the number of MLEM patents in each country using SPSS 23.0.

3.1.3 Results

Of the 375 items on the 2013 MLEM, 20 drugs (or about 5%) had some kind of patent protection in at least one of the 137 developing countries. Our study found 1,735 patents overall, but one-third of the countries ($n=44$) had no filings whatsoever. The number of MLEM patents per country was significantly positively associated with HDI, GDI per capita, total healthcare expenditure per capita, population size, the Rule of Law Index, and average education. Population size, GDI per capita, and healthcare expenditure (in % of national expenditure) were predictors of the number of MLEM patents in countries ($p=0.001$, $p=0.001$, $p=0.009$, respectively). Population size was the most important

predictor ($\beta=0.59$), followed by income (GDI per capita) ($\beta=0.32$), and healthcare expenditure ($\beta=0.15$).

3.1.4 Conclusion

Companies tend to file patents wherever markets are large, i.e., countries with large populations, especially those with relatively more wealth. Our finding regarding the importance of population size, above monetary value, contributes a deeper level of nuance in understanding the patterns of essential medicine patent filing behaviors internationally. While we found that the overwhelming majority of MLEM products are post-patent, there are some patents on essential medicines that are indeed in force, apply to a large proportion of those living in the developing world, and therefore hold high public health importance. We recommend that the essential medicine patent situation continue to be monitored in developing countries, as has been done in this study.

3.2 Introduction

The World Health Organization's (WHO) Model List of Essential Medicines (MLEM) (1) identifies effective health products that all persons should, at a bare minimum, have access to, regardless of where they live or how much money they have. Updated biannually, the products appearing on the MLEM are typically older and off-patent. However, over the past 15 years, several newer medicines for treating HIV and other diseases have been added to the list (2). As these medicines were both patented and expensive, friction arose between advocates of intellectual property protection and advocates of essential medicine access (3). These debates continue today and extend beyond HIV to other disease burdens, such as hepatitis C and cancer (4, 5).

Price is one determinant of access to essential medicines. As prices may be elevated where patents are protected, patent protection may indirectly impact access (6). To understand the extent to which patents may have such an indirect influence upon essential medicine access at the international level, it is critical to have exact data on where manufacturers have filed patents on MLEM products globally (7, 8). Simply put, it is only where patents exist, either locally or in the manufacturers' countries, that it is logically and legally possible for patents to complicate access. Therefore, previous studies have focused on surveying the essential medicine patent landscape using contemporaneous editions of the MLEM (i.e., 2003 (9), 2009 (10), and 2011 (11)). This article details statistical analyses performed upon the data collected during the fourth study to follow in this tradition using the 2013 MLEM, which was published by the World Intellectual Property Organization (WIPO) in April 2016 (12, 13). The present article's research question is: in which developing countries are patents on essential medicines being filed?

3.3 Methods and materials

The international patent data collection was completed in three phases: (i) identifying which medicines from the MLEM could be considered “patented” using the United States Food and Drug Administration’s Orange Book (14), Health Canada’s Patent Register (15) and Drug Product Database (16), and previous studies (9-11); (ii) linking these patent data to related patents abroad using international patent databases (INPADOC (17) and Derwent (18) via Thomson Innovation (19)) and creating a preliminary landscape report; and finally (iii) approaching each medicine supplier with our preliminary data and requesting their feedback. Nine of 11 companies participated in the study. We then organized our data into a table with the 20 MLEM medicines that we had found to be patented as the row headers (horizontally), the developing countries (n=137) as left column headers (vertically), and then tallied number of patents relevant to each drug-country combination. (Note we excluded countries categorized by the World Bank as “High” income or as having “Very High” development designation by the United Nations to keep the focus on developing countries (20, 21).) This data table served as the basis for our statistical analyses. This table and more details on our methodology for this phase of the study are available in the full WIPO report (13).

Statistical analyses were carried out using SPSS 23.0 (22). A p value <0.05 was considered significant. Spearman correlations were done to assess bivariate relationships between variables. A multivariate regression model was developed to explain the number of MLEM patents in each country. Robust multivariate regressions were performed using the bootstrap procedure to ensure accurate and generalizable results because some variables were not normally distributed (23). Variables to be included in the model were selected *a priori* on a theoretical basis to avoid overfitting the data (23). Indeed, the model was built upon previous evidence suggesting that patent filings follow high-value national markets (9,

10). Selected variables were population size (in millions), GDI per capita, and total healthcare expenditures (as a percentage of GDP) (21, 24). Total healthcare expenditures as a percentage of GDP was chosen instead of total healthcare expenditures per capita because of multicollinearity between this last indicator and GDI per capita. Absence of multicollinearity between independent variables was assessed using a variance inflation factor test. In additional models, we further adjusted for the Gini Index (25), and the Rule of Law Index (26), separately. The Rule of Law Index is a composite score compiled by the World Justice Project and may be suggestive of the general strength of countries' legal systems, though intellectual property law is not given specific consideration. As patents confer the right to patent holders to pursue financial compensation from infringers in law courts, we hypothesized companies may be more likely to file patents in countries where the legal system is strong (and the Rule of Law Index score is accordingly high). In both cases, the additional determinant (either Gini Index or the Rule of Law Index) was not significant, other determinants were similarly associated with the outcome and we lost some statistical power (n decreased from 129 to 60 and 69, respectively). Therefore, we present only the original model in the paper. Standardized beta values were used to provide insight into the relative importance of predictors in the model (23).

3.4 Results

Of the 375 items on the 2013 MLEM, we found that 20 drugs (or about 5%) had some kind of patent protection in at least one developing country. Across the 20 drugs and 137 countries, we found 1,735 patent filings overall. Most of these medicines were for HIV/AIDS (13 of 20); the remaining ones were antibiotics, other anti-virals, or were for non-communicable diseases (cancer and gastroesophageal reflux disease).

We found that the 20 patent portfolios (i.e., the global list of patents for a given drug) varied greatly in their number (range: 1 – 173 patents; median: 48 patents) and their

geographic reach (ranging: <1 – 44% of developing countries; median: 15% of developing countries). One-third of the countries (n=44) had no essential medicine patent filings whatsoever. Oppositely, Table 3.8.1 shows the top-10 countries where we found the most essential medicine patent filings.

Correlation between the number MLEM patents per country, number of MLEM drugs patented per country, and development indicators are presented in Table 3.8.2. As expected the number of MLEM patents and the number of MLEM drugs patented per country were highly associated ($r=.995, p<0.0001$). Consequently, and for brevity, we only discuss the number of MLEM patents per country from now on. The number of MLEM patents per country was significantly positively associated with population size, GDI per capita, total healthcare expenditure, HDI, average education, and the Rule of Law Index, but it was not associated with the Gini Index or life expectancy at birth.

Table 3.8.3 presents the multivariate regression model predicting the number of MLEM patents per country. Population size was the most highly significant positive predictor of the number of MLEM patents per country ($p=0.001$), followed by income (GDI per capita) ($p=0.001$), and total healthcare expenditure as a proportion of the Gross Domestic Product (GDP); $p=0.009$).

Based on standardized beta values, population size was the most important predictor of the number of patents in a country ($\beta=0.59$). Holding the other two factors constant (income and healthcare expenditure), an increase of 1 million persons was associated with an increase of 0.07 essential medicine patent filings. GDI per capita was the second strongest predictor and was about half as strong as the population variable ($\beta=0.32$). An increase of \$1000 GDI per capita was associated with an increase of 1.2 essential medicine patent filings when holding the other two factors constant (population and healthcare expenditure). The healthcare expenditure variable was the least strong

predictor and was about half as strong as was GDI per capita ($\beta=0.15$). Holding the other two factors constant (population and income), an increase of 1% of GDP spent on healthcare was associated with an increase of 1.14 essential medicine patent filings. This model accounts for 44% of the variance in the number of MLEM patents per country ($r^2 = 0.44$).

3.5 Discussion

As expected, the overwhelming majority of medicines on the 2013 MLEM were older and post-patent. Still, we found that patents were filed for a subset of 20 drugs on this MLEM. Generally speaking, companies appeared to be filing essential medicine patents according to countries' potential market size, which is also consistent intuition based on previous studies. Countries' population size, income and healthcare expenditure served as a good proxy for potential market size. With just these three variables, our model explained 44 percent of the variance in the number patent filings across the 127 developing countries in our sample for which development data were available. This level of variance is comparable to that of previous studies (9), but applies to a sample that is more than three times larger. We further found that, based on standardized beta values, population size was an even stronger predictive variable in our model relative to the monetary indicators (which were also highly statistically significant). This finding regarding the relationship between population size and the number of patent filings is consistent with others' observations in other sectors and contexts (27).

What is the significance of this finding? With respect to the literature, previous emphasis within the access to medicines vis-à-vis patent protection debate has been put more heavily upon countries' wealth (3, 9-11). While our study corroborates the importance of these economic indicators, we also found that population size seems to be a critical determinant of where companies file medicine patents. The importance of population size, above monetary value, contributes a deeper level of nuance in

understanding the patterns of essential medicine patent filing behaviors internationally. Our finding is that, controlling for the economic variables, there was 1 additional essential medicine patent per every increase of 14.29 million people in the national population. Many of the developing countries covered by our study have smaller populations and we observed that patents are rarely filed there, even in those where wealth is relatively high (e.g., Belize, Dominica, Fiji, Grenada). Indeed, of the world's 233 countries, only 75 currently have a population larger than 14 million; in other words, the implication is that about two-thirds of the world's countries have populations too small to motivate companies to file many pharmaceutical patents there. Of course, we also found the opposite to be true. The highest number of essential medicine patent filings were typically in the developing world's most highly populated countries (though there are some major exceptions, such as Bangladesh). For instance, India, Indonesia, and the Philippines appear in the top-10 list in Table 3.8.1, even though they have relatively low incomes per capita. The upshot is that concerns surrounding medicine patent filings are fairly specific to a subset of the developing world's countries that have very large populations, rather than to the majority of developing countries. As this subset of countries have populations large enough to sustain domestic pharmaceutical production, companies' tendency to file patents in these regions is likely reinforced since many of these same countries are major exporters of medicines to low- and least-developed countries.

3.5.1 Implications for the debate on access to medicines vis-à-vis patent protection

Our findings regarding population size are informative for both sides of the debate on access to essential medicines vis-à-vis patent protection in developing countries.

It is important for critics of the patent system to remember that companies' motives behind patent filing may be about more than just securing exclusive markets in order to charge exorbitant prices. Patent filing is a standard procedure for companies distributing

their products in any jurisdiction. Due diligence requires that they secure the legal freedom to operate wherever they intend to enter markets. Filing for patents will minimize the risk of infringement lawsuits in the event that another party has also laid claim on the same intellectual territory. This rationale for patent filing to minimize liabilities will be strongest where population sizes are large. The monetary value of these markets is related to and reinforces this trend. From this perspective, then, patent filings could be one signal of companies' intentions to make their product commercially available in the region in question.

On the other hand, it is important for advocates of the patent system to remember that patents are typically filed wherever there is a large market, which largely has to do with population size as well as wealth. Therefore, the number of patents and the number of legal jurisdictions covered by them is not necessarily indicative of their importance for access to particular essential medicines from a global population perspective. For example, two effective patent filings for a particular product in India (population: 1.3 billion) and China (population: 1.4 billion) could have substantial impacts for the developing world since these countries have disproportionately high numbers of persons residing there. And this is not to mention that these countries are also medicine-exporting countries, which lower income countries rely upon for medicine supplies. A few well-placed medicine patents, therefore, could have an enormous impact upon the developing world's access to particular essential medicines. Given that India is a major generic pharmaceutical manufacturing center, a patent in India can be tantamount to a patent in much of the developing world. While this concerns an admittedly small subset of the MLEM at the moment, these drugs are of serious global public health interest in specific cases (e.g., curative treatments for hepatitis C) and their importance should not be minimized.

3.5.2 Policy implications

Regardless of which side of the ideological debate readers may identify with, we believe the way forward is the same.

We recommend that the essential medicine patent situation continue to be monitored in developing countries, as has been done in this study. While we found that the overwhelming majority of MLEM products were post-patent, there are some for which patents are indeed in force in regions where a large proportion of the developing world resides. Further, there are many good reasons to suspect that the MLEM patent situation will become much more complex in the future. For example, the demographic profiles (and their corresponding epidemiologic profiles) of middle-income countries are becoming increasingly similar to those of rich countries, meaning that these populations increasingly share many of the same disease burdens and demands for the same pharmacologic solutions (30). Another contributing factor for this epidemiologic convergence may be the increasing level of trade between rich and poor nations. Disease has followed trade routes throughout human history (31). Studies have found positive associations between the increase of free-trade agreements in developing countries which facilitate elevated consumption of tobacco, alcohol, sugar, and processed foods, and an increase in related non-communicable diseases (32). Therefore, as the MLEM is revised in the future, the products added may be more often under some form of patent protection, especially as developing countries grow in wealth. Indeed, our preliminary appraisal of the 2015 MLEM found that the number of patented medicines had nearly doubled since 2013, and included several new cancer drugs (12, 13).

Such monitoring of the essential medicine patent situation would ideally be done in cooperation with global pharmaceutical suppliers as they are uniquely positioned to know where they have filed patents and where they intend to enforce them. Most companies

eventually participated in our study (Only Cipla outright refused (33); the other firm, InSite Pharmaceuticals, was non-respondent). We recommend that companies follow the examples of Merck KGaA (34), GSK (29), and Novo Nordisk (35) by proactively and transparently disclosing information on their international patent holdings. These data will facilitate surveillance studies for maintaining an accurate picture of the MLEM patent landscape. This transparency will also keep healthy pressure upon companies to ensure reasonable access to new MLEM products where they hold relevant patents (36).

The data disclosed by companies would ideally include the patent numbers grouped by the type of protection covered (e.g., active ingredient, manufacturing process), exactly in which developing countries companies intend to enforce those patents, when those rights expire, and what the companies are doing to mitigate access challenges through sustainable access initiatives as new products are rolled out internationally (e.g., official statements of patent non-enforcement in certain regions, licensing agreements with generic suppliers, tiered pricing schemes) (12, 13, 36-40). As noted previously, compiling this information into an international register would be optimal. This would not only be instrumental for researchers, but with the problem areas precisely and explicitly identified, patent filings could serve as springboards for cooperative access campaigns, rather than as adversarial barriers.

3.6 Conclusion

Most drugs on the 2013 MLEM were post-patent; however, an important, yet small subset of these medicines were indeed newer and relevant patents were in force in a subset of developing countries with large potential pharmaceutical markets. The importance of population size as a predictive variable of where companies tend to file essential medicine patents—even above economic ones—contributes a deeper level of nuance in understanding the patterns of essential medicine patent filing behaviors internationally.

Isolating the key essential medicine patents through surveillance studies, therefore, is a critical activity that should continue into the future, as the MLEM is updated to reflect our world's evolving demographic and health needs. Companies can facilitate this process by participating in studies like this one and/or by transparently making their data on their international essential medicine patent holdings publicly available. It stands to good reason that those working in the health sector and benefiting from the patent system would do their part to proactively and transparently minimize wherever the two (i.e., health and patent protection) may come into conflict.

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3.8 Tables

Table 3.8.1 Top-10 developing countries for MLEM patent filings

1. China	6. Brazil
2. Mexico	7. Turkey
3. Romania	8. India
4. Philippines	9. South Africa
5. Bulgaria	10. Indonesia

Table 3.8.2 Spearman correlation coefficients (*r*) between MLEM patents and development indicators

	Total MLEM patents	MLEM drugs patented	Population	GDI per capita	Total healthcare expenditure per capita	HDI	Average education	Rule of Law Index	Gini	Life expectancy at birth	Total healthcare expenditure % of GDP
Total MLEM patents	1	.995***	.441***	.241**	.256**	.232**	.268**	.326**	.102	.103	.121
MLEM drugs patented	137	1	.457***	.267**	.276**	.255**	.277**	.327**	.129	.133	.114

p* < 0.05, ** *p* < 0.01, * *p* < 0.001.

Table 3.8.3 Linear regression model of predictors of number of MLEM patents in developing and emerging countries (n=129)

	<i>b</i> ^{1,2}	SE <i>B</i> ²	β	<i>p</i>	R ²
Constant	-5.95 (-14.10, 1.31)	4.45			
Population (in million)	0.07 (0.05, 0.20)	0.01	.59	<i>p</i> = 0.001	
GDI per capita (in 1000\$)	1.20 (0.55, 1.77)	0.26	.32	<i>p</i> = 0.001	
Total healthcare expenditure (% of GDP)	1.14 (0.38, 2.16)	0.54	.15	<i>p</i> = 0.037	
Model R ²					0.44

¹ 95% bias corrected and accelerated confidence intervals reported in parentheses

² Confidence intervals and standard errors based on 1000 bootstrap sample

Chapter 4 (Article 3):

**Accelerating access to generic HIV medicines in developing countries that have
granted patent protection**

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4.1 Background

4.1.1 Abstract

Patent protection on medicines may frustrate access by blocking generic competition. Nevertheless, circumstances may allow for generic procurement to be made anyway, especially for humanitarian cause. But to what extent is this being done? And what legal flexibilities are facilitating such generic procurements?

4.1.2 Methods and materials

We linked all company-verified antiretroviral (ARV) patent data (1,260 patents for 12 drugs) from a World Intellectual Property Organization patent study on the 2013 World Health Organization's (WHO) Model List of Essential Medicines to all available matching procurement records in the WHO's Global Price Reporting Mechanism. We then cross-referenced these with lists of legal flexibilities which facilitate generic access where patents have been granted (e.g., supplier companies' patent non-enforcement policies, and voluntary and compulsory licenses).

4.1.3 Results

The patent status of 1,924 generic procurements transactions (1.34 billion units) from 85 countries was investigated. Over half (53%) of the generic procurement was either exported from and/or imported to a country with relevant patent protection. A variety of legal flexibilities likely facilitated these generic procurements, though voluntary licenses appeared to be the most commonly used.

4.1.4 Conclusion

Despite the fact that patents are relatively less common in the resource-poor settings, they are still highly salient to generic access in the developing world because they have been filed in medicine-exporting countries and/or those with very large populations. Nevertheless, many generic procurements were made within the context of patent

protection. A variety of legal flexibilities were likely utilized to facilitate this. As voluntary licensing was the most often applicable flexibility, accordingly strong focus should be put on getting these arrangements right to ensure public health is kept as a core concern.

4.2 Introduction

An increasing number of international medicine patent landscapes are available online and in academic journals (1-12). These studies identify and compile lists of patents internationally for a given product or set of products. Such studies began within the context of the debate between advocates of patent rights and of medicine access during the beginning of the global campaign for HIV, malaria, and tuberculosis medicines. The concern is that patent protection may exclude generic competitors from market entry and enable suppliers to keep prices above what payers in developing countries can afford, thereby frustrating medicine access and causing ethical concerns. Patent studies were therefore conducted to estimate the potential for medicine access to be complicated by patent protection by locating exactly where in developing countries medicine patents had been filed. Several studies (2, 4, 9) have found that medicine patents are far less common in low-income countries than in wealthier ones—the implication has been that there is substantially less potential for medicine access and patent protection to conflict in resource-poor settings than in wealthier countries.

While these patent studies contributed much-needed empirical precision to the debate, they did not go far beyond counting the number of patents that had been filed on key medicines and the number of countries covered by them (some additionally documented which patents were on the active ingredients, which are more likely to block generic competition). There are at least two reasons why relying on the patent data alone could distort estimates of the potential for where patent protection and medicine access might come into conflict. First, while patents are granted on a country-by-country basis, the populations and manufacturers are not equally distributed across them. Just two medicine patents filed, for example, in India or China could have substantial global health impact since a large proportion of the developing world resides there (1.3 billion and 1.4 billion

respectively) and since both of these countries are major exporters of generic medicines to other developing countries. Importing countries' generic availability, therefore, can be impacted by patent protection in the exporting country abroad, even when there is no relevant patent protection in force domestically whatsoever. From this perspective, relying only on the lower number of patents and of developing countries covered by them—without taking into account the unequal distribution of populations and medicine exporters—may *under-estimate* the potential for where patent protection and medicine access might come into conflict.

On the other hand, patents often do not actually block generic competition in reality, even in the United States and Canada where linkages between the patent system and drug regulatory bodies are strong (13). A recent patent study of cardiovascular medicines found that of the 24 medicines for which patents appeared in the medicine patent registers of the United States or Canada, generic equivalents were readily available in the respective country for 16 of these medicines (66.7 percent) (14). A number of circumstances may allow for generic competitors to be present in the same markets where valid patents are in force. For example, a patent on a process for manufacturing a medicine does not preclude others from using different processes for making and selling the same medicine. Further, most countries leave it to the patent holders to enforce their exclusive market rights by taking infringers to court (15). Therefore, should generic suppliers conduct their own legal assessment and identify weak or invalid medicine patents, these companies may make a calculated decision to enter the concerned medicine markets anyway and infringe, confident that they will win if challenged in court by the patent holders. These situations are common in medicine markets and help the patent system self-regulate, as dubious patents will be ignored or challenged (11). From this perspective, relying primarily on the number of patents and countries covered by them—without taking into account the many

circumstances in which patents do not block generic competition—may *over*-estimate the potential for where patent protection and medicine access might come into conflict.

Further, when it comes to global health, there are additional legal flexibilities that give more reason to suspect that generic medicines may still be accessible even where patents have been granted. First, members of the World Trade Organization (WTO) with Least-developed Countries (LDCs) status have been given an extension until 2033 to align their medicine patent laws with the requirements of the Trade-related Aspects of Intellectual Property Rights (TRIPS) Agreement, meaning that there may be more flexibility for LDCs to procure generics even if they have also granted patents on those same medicines (16, 17). Second, originator companies of brand name products have begun to voluntarily license generic manufacturers to supply their products in certain developing countries in exchange for a negotiated royalty rate (18, 19). Third, on occasions when the public health demand for a key medicine is extremely high and originator companies are unwilling to license other suppliers to meet that need, countries may take action to bypass patent protection in order to authorize generic procurements or generic suppliers to enter the market; this flexibility is called compulsory licensing (20). Fourth, originator companies may publicly declare their intention to refrain from enforcing their patents on key medicines for global health (e.g., antiretrovirals (ARVs) for treating HIV) in specific regions of the developing world, so that generic suppliers can proceed there without fear of legal recourse (18).

In sum, the number of patents and countries covered by them might under- or over-estimate the extent to which medicine patents might block generic competition in the real global marketplace, especially within the context of humanitarian cause. Recent debate on this subject has signaled the need for further research in this area (13, 21, 22). It is now possible to address this knowledge gap for global health by linking patent data available

through the World Intellectual Property Organization (WIPO) with international procurement data on ARVs available through the World Health Organization (WHO). It is also possible to link these data to those on the use of the aforementioned legal flexibilities. This article, therefore, seeks to address this knowledge gap through linking these datasets. The main research question is: To what extent can developing countries that have granted patent protection still procure generic medicines? And what legal flexibilities may have facilitated this access?

4.3 Methods and materials

4.3.1 Selection of ARVs and patent data collection

For our product selection, we relied upon our previous study (9, 23) of the 2013 WHO Model List of Essential Medicines (MLEM) (24), which identified 13 ARVs that are likely to be under patent protection in some developing countries. This identification was done by using the national medicine patent registers of the United States (25) and of Canada (26). We then linked these American and Canadian patent data to the equivalent and related ones abroad contained in the INPADOC (27) and Derwent (28) international patent databases by using the Thomson Innovation platform (29). These databases group related patents internationally into “families” (30). The union of the INPADOC and Derwent patent families for each product served as our initial list of patents. As this linkage technique is known to have some imprecision (31), we consulted the global supplier companies of these drugs so that they could correct and validate our results. After some persistence, all companies cooperated, except for Cipla for its product Triomune (9, 23); we therefore excluded this medicine, and consequently, a total of 12 ARVs were included in our study. Our complete methodology for the product selection and patent data collection as well as our product sample and patent dataset have been published in the full World Intellectual Property Organization (WIPO) report (9).

4.3.2 Linking the patent data to international procurement data

We next matched the patent data for each of the 12 ARVs to the corresponding procurement data contained in the WHO's Global Price Reporting Mechanism (GPRM) (32) for the identical time period as the patent study (January 2014 – August 2015). We matched the data according to the active ingredient, formulation, and strength. The GPRM aggregates ARV procurement data on buys made with assistance from international actors from the international market by (or on behalf of) developing countries. Others have used this database to investigate international ARV procurement costs and related policy issues (33-37). For each procurement transaction, the GPRM indicates the exporting and importing countries, the supplier, and whether the product was generic or was the originator's brand name product. With these patent and procurement data linked, we could then observe to the extent to which generic products were supplied despite the presence of patents in the importing and/or exporting countries.

4.3.3 Linking the patent and procurement data to possible use of legal flexibilities

Next, for each subset of generic procurements made in areas where there was relevant patent protection, we cross-referenced the particular ARV, the supplier company, and/or countries with data on the legal flexibilities that we described in the introduction. This enabled us to triangulate what flexibility (or flexibilities) may have been relevant and may have facilitated the generic procurement where patent protection had been granted. To be clear, this exercise is to estimate possible use of the flexibilities, not document actual use (as that would require an extensive validation procedure that is not feasible given the volume of transactions contained in our dataset). In Table 4.8.1, we have indicated the flexibility with a description of how we matched these with our patent and procurement data.

4.3.4 Analyzing the complete dataset

With product and patent data linked to the procurement data and to the corresponding legal flexibilities, we next compiled descriptive statistics to provide direct answers to this study's research questions. Our results and observations are outlined below.

4.4 Results

After completing above described protocols for identifying products and for collecting international patent data, there were 1,114 patents corresponding to one of the 12 ARVs included in our study. The GPRM contained 2,536 procurement transactions (a total of 1.51 billion units) from 85 countries for these 12 ARVs. The overwhelming majority (90% or 1.34 billion units) of these procurements were generic medicines.

4.4.1 Generic procurements for/from countries that have granted patent protection

As is shown in the “patents” bar in Figure 4.9.1, more than half (53% or 716 million units) of these generic procurements took place where there was patent protection for the ARV in question—either on the exporter's side (31% or 219 million units), the importer's side (52% or 376 million units), or on both sides (17% or 121 million units). The “no patents” bar in Figure 4.9.1 shows that less than half (47% or 628 million units) of these generic procurements recorded by the GPRM for our sample took place in areas void of relevant patent protection (i.e., there was no relevant patent protection in either the importing country or in the exporting one). Our main observations for Figure 4.9.1 are that generic procurement appeared to be slightly more common where there was patent protection than where there was none, and secondly, that many procurements were made with patents being present in the exporting country, but not in the importing country.

4.4.2 Generic procurements and patent presence by importing countries' level of development

Reasoning that others have observed that patents filing are positively associated with countries' level of development (2-4, 9), we stratified this same data in Figure 4.9.2 by the importing countries' Human Development Index (HDI) score (38). The blue bars represent the proportion of generic units that were procured with relevant patent protection in either the importing and/or exporting country whereas the red bars represent those that were made without patent protection on either side. The actual total number of units (TNUs) are noted in the chart below the bars. We have also plotted and listed the proportional shares of patents, HIV patients, and TNUs categorized by the importing countries' HDI score. Note that the share of TNUs has a similar slope to the share of HIV patients, but with heavier emphasis upon the low HDI countries; this is appropriate given the humanitarian context of these procurement data.

Significantly, Figure 4.9.2 shows that the proportion of transactions within the context of patent protection is much higher than the proportion of patents for those HDI groups (i.e., the blue bars extend much higher than the green lines). For example, even when the importing country had a low HDI—where the share of patents included in our study were far less common (only 12%)—there was still relevant patent protection pertaining to nearly half (48% or nearly 519 million units) of these countries' procurements. This result is driven by two factors: there were more active patent filings in countries with larger HIV populations (e.g., Nigeria); and secondly, these countries procured their generic ARVs from India, where active patent protection was in place for several of the products in our sample. Indeed, of the nearly 519 million units of generic products bought by low HDI countries shown in Figure 4.9.2, 29% were instances wherein the patent protection was exclusively on the exporter's side (i.e., there were no relevant patents

whatsoever domestically). Our main observation for Figure 4.9.2 is that the distribution of populations and medicine exporters across countries does indeed seem to matter; a few well-placed patents in medicine-exporting countries with large populations can have a disproportionately high relevance to international generic medicine trade in the developing world, even though patents are rarer there.

4.4.3 Legal flexibilities that may have facilitated the generic procurements

Given our observation that generic procurements were common where there was patent protection, we next investigated what legal flexibilities might have facilitated these transactions in the subset of generic procurements that were made within the context of patent protection (i.e., 716 million units). See Table 4.8.2. The largest number of TNUs (79%) corresponded to voluntary license agreements, such as those multilateral arrangements done in cooperation with the Medicines Patent Pool. About 22% of the TNUs were directed to countries with LDC status. An important caveat for Table 4.8.2 is that more than one of legal flexibility may have applied for some procurements. VLS, for example, typically include all LDCs, and some CLs may have been issued within regions that were already covered by relevant VLS.

In Figure 4.9.3, however, we examined the extent to which each policy may have uniquely expanded the territorial coverage of flexibilities allowing for generic procurements within the context of patent protection; in other words, we corrected for the redundancies where more than one policy may have applied. We did this by ranking the flexibilities by their applicability to the lowest income countries by beginning with the LDC waiver as the reference. Specifically, we counted how many units may have been relevant to non-assert policies, but not to the LDC waiver; then how many units may have been relevant to VLS, but not to the LDC waiver nor to companies' non-assert policies; then how many

units may have been relevant to CLs, but not to the LDC waiver, non-assert policies, nor VLs; and finally, how many units were relevant to none of these.

Figure 4.9.3 shows the breakdown of this count by ARV. Panel 1 shows the overall possible applicability of the legal flexibilities in absolute terms. The VL category clearly still had the largest potential relevance after correcting for the redundancies, but the LDC waiver and the “other” category were also large. As for the “other” category, one study (39) noted specific examples of companies known to be selling generic versions of branded drugs without a VL or a CL; while circumstances may have changed since that publication, these same companies and products corresponded to 12% of those procurements in our “Other” category. We discuss this in more detail below. Our main observation for Panel 1 (as well as Table 4.8.2) is that, generally speaking, VLs seemed to have the largest potential relevance in this sample of ARVs for facilitating generic procurement by developing countries that had granted patent protection, even when we removed the overlap with other flexibilities like the LDC waiver.

Panel 2 in Figure 4.9.3 shows the possible applicability of the legal flexibilities by ARV proportionately, rather than in absolute terms. It shows the diversity in the relevance of these policies across the sample of medicines. For example, companies’ non-assert policies may have been highly relevant for atazanavir and didanosine, but not others. CLs may have added some relevance for efavirenz, but not far beyond the regions already covered by the LCD waiver and VLs. Our main observation for Panel 2 is that the relevance of the flexibilities varied by product and originator company; VLs were not always the most potentially applicable flexibility in this sample.

4.5 Discussion

Our study has provided one snapshot of international medicine procurement for a sample of essential ARVs paired with data on corresponding patents and legal flexibilities

within the context of the global campaign for HIV medicine access. We observed in our dataset (i) that it was slightly more common for generics to be purchased where there is some form of relevant patent protection (53%) than where there is none (47%); (ii) that the number of patents and countries covered by them is not necessarily indicative of their potential to influence to medicine access internationally since patents can be placed in medicine-exporting countries and/or in those with very large populations; (iii) that voluntary licensing practices may have been the most heavily relied upon flexibility generally speaking for facilitating generic procurement, but that other flexibilities were sometimes more important (e.g., the LDC waiver, non-assert policies). These results are informative for both sides of the medicine access vis-à-vis patent protection debate as was presented in the introduction. We discuss these nuances for the research and policy debate below.

4.5.1 Low patent counts are not necessarily equivalent to low relevance for access

Previous studies have demonstrated that patents are less common or even relatively scarce in low-resource settings (2-4, 9, 23). Based on this empirical patent data, it is tempting to conclude that patent protection is not very relevant to low-income countries. Some advocates of medicine patent protection have taken comfort in this point. The procurement data, however, shows that it does not take many patents (and countries covered by them) to potentially influence generic medicine trade substantially since patents can be placed in medicine-exporting countries and/or those with very large markets. Therefore, estimations of the relevance of medicine patent protection to developing countries can indeed be underestimated if the unequal distribution of populations and medicine exporters in the developing world is not taken into account. This is notable for future research. Advocates of medicine access do have grounds for concern, despite the relatively low number of medicine patents in low-income countries. After all, it was more

common in our sample for procurements to be made within the context of patent protection than outside of it.

4.5.2 Patents are not necessarily equivalent to generic access barriers

On the other hand, advocates for medicine access should note that patents often do not block generic competition. Our study shows generic buys were common in the international market, even when patent protection was in place, both on the supplier side and on the importer side. This result aligns with those of our previous findings regarding the presence of generics in the United States and Canada, despite patents being listed in those countries' medicine patent registers (13, 14); therefore, this phenomenon is not necessarily limited to the developing world. This finding matches general marketplace intuition in many respects. Patent filings are part of the business and marketing strategies of pharmaceutical suppliers. Filing patents to secure the legal freedom to operate is a standard and routine feature of procedural due diligence and minimizing infringement liabilities, regardless of a company's chances at establishing an exclusive market. As such, patent filings internationally are likely to follow the same patterns as medicine trade flows internationally (9). Generic competitors follow these same currents in pursuit of market and manufacturing prospects. From this perspective, therefore, one should expect to observe a reasonable degree of similarity between trends in medicine patent filings and of generic drug sales in developing countries.

4.5.3 Voluntary licenses can facilitate generic medicine access for low-income countries

Further, our finding regarding the large potential relevance of VLs is noteworthy vis-à-vis the finding that generic procurements were actually slightly more common within the context of patent protection. If true, the implication is that VLs could actually enhance generic access; in other words, rather than being managed just as barriers, patents can also

actually serve to create the grounds for very productive cooperations between companies for bringing high-value medicines to lower income countries more expeditiously than would have otherwise been the case. And as many VL agreements include technology transfer from the originator companies to the generic ones, these collaborations could foster meaningful capacity building amongst generic firms based in developing countries. This is a major advantage of VLs over the other flexibilities discussed in this paper since these arrangements include the transfer of non-patent know-how and show-how, including trade secrets and other intellectual property that is not disclosed in the patent(s) and that is imperative for successfully manufacturing a very high quality generic equivalent to the originator product (55). Furthermore, should voluntary licenses offer genuine benefits to originator companies, there is no reason to suspect that such arrangements will be confined to HIV medicines. Indeed, some companies have already been using them for HCV and other illnesses (41-42).

Given the high use of VLs, accordingly strong attention should be put on these arrangements and getting them right. VLs can certainly have their pitfalls, such as unreasonable anti-diversion programs that require patients to have citizenship within the covered territories (40). Geographic scope will always be a point of contention wherever the line is drawn (41, 42). However, if public health is kept as the core focus and if powers are balanced at the negotiating table, mutually beneficial VL arrangements can be found and can be a significant vehicle for accelerating access to critical medicines (23). Encouraging transparency on these agreements will be imperative for accumulating knowledge and experience on how to best design these licenses and make them work for public health.

As experience accumulates, it might be possible to envisage novel ways to creatively leverage VL agreements for development whenever royalty free licenses are infeasible. For example, Merck (MSD) made a VL agreement with a generic company to sell efavirenz in

South Africa. The contract called for the royalty fees to be paid to a charitable foundation (43). A variation of this design could be to direct royalty funds instead to projects to address the “pharmaceutical gaps” (i.e., the essential medicine “wish list”) identified by the WHO (44, 45). Such a design could be particularly promising if utilized through a multilateral patent pool like the Medicines Patent Pool (46), given the number of VLs that they maintain. Funds could be directed to a research and development (R&D) utility like the Drugs for Neglected Diseases Initiative (www.dndi.org). In doing so, the patent system could be leveraged to bring additional funding to areas where it normally fails to incentivize drug development. In our sample of procurement data, a total of \$86.79 million was spent within zones covered by VLs; even a royalty of 5% for this small sample would direct \$4.34 million to supplement R&D or to fund clinical trials for neglected disease per year.

4.5.4 Other facilitators of generic access

Another noteworthy finding from this study is that other flexibilities were sometimes more relevant than VLs (see Panel 2 in Figure 4.9.3). Waivers for LDCs likely played central and core role. Non-assert policies were critical for atazanavir and didanosine. CLs were key for some countries, especially for efavirenz. No single flexibility, or combination of flexibilities, seemed to have been equally applicable across all medicines. What works best for minimizing costs and maximizing quality likely varies by the particular circumstances (22). We therefore recommend maintaining a diversity of available approaches; in other words, the redundancies of legal flexibilities for low-income countries to procure generic medicines is valuable.

Indeed, the “other” category was key for some ARVs. Certainly, generic companies operating within humanitarian contexts may have some additional confidence that originator companies are less likely to take legal action for infringement and may proceed accordingly. Further, compound patent protection on many of the products in our sample

has expired (e.g., abacavir, tenofovir) in most countries (47). As mentioned in the introduction, other forms of patenting, such as (co-)formulation patents, are less effective at dissuading generic competition. Generic suppliers may enter markets based on their own legal assessment of the relevance or quality of the patents that they are potentially infringing since there is not strong linkage between the drug regulatory system and the patent system in most of the world. In doing so, weaker patents are less likely to confer market exclusivity. Maintaining this kind of flexibility (as well as direct patent challenges) is critical for patent systems to self-regulate, as it is possible for patents to be granted that should not have been (11).

4.5.5 Limitations

This study is only one snapshot within the context of the global campaign for HIV medicines, and it includes some older (albeit still patented) ARVs in its sample. It is worth repeating studies like this one in order to determine whether the results hold with different samples of medicines, patents, and procurements. To gain insight into the generalizability of these results, replications using samples of medicines outside of the HIV context would add great value. Advances in medicine procurement transparency and medicine patent transparency are critical to this end. Should it be determined that these results are specific to the HIV context, it might be time to consider whether the procurement system that has been hammered out for HIV could be scaled up to include other essential medicines and could serve to significantly reduce potential conflicts between patent protection and access in developing countries in the future.

4.6 Conclusion

This study has been one attempt to gain insight into the extent to which generic medicines can be procured by developing countries that have granted patent protection. This subject is important now and will become even more important in the future. More

patented medicines are being added to the WHO's Model List of Essential Medicines (9). Further, more WTO members who are key medicine-exporting countries (e.g., India) are now observing higher levels patent protection than a decade ago. This will bring unprecedented challenges and opportunities. While we found that a few patents filed in key markets and medicine-exporting countries can potentially have a large impact on generic medicine access, we also found that many countries are still able to procure generic medicines. VEs and other flexibilities can facilitate these buys. Rather than managing patents as barriers to medicine access, it is also valuable to investigate ways in which patents may serve as springboards for novel access initiatives and how the current system could be leveraged to better facilitate and accelerate access to medicines in developing countries. After all, access is ultimate goal, regardless of one's ideological leanings with respect to the patent system.

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4.8 Tables

Table 4.8.1 – Legal flexibilities investigated as potentially relevant to generic procurements where patents were granted

Flexibility	Description	Matching method	Example	Data sources
LDC waiver	LDCs have postponements for TRIPS-level medicine patent protection, which may allow extra flexibility to procure generics even though patents have been granted	We cross-referenced the importing country in the procurement data with the contemporaneous list of countries with LCD status.	Generic procurements of abacavir were made by Uganda, which has granted relevant patents. Uganda has LCD status. Therefore, we counted the LCD waiver as potentially relevant.	The contemporaneous list of countries with LDC status (16, 17, 48)
Non-assert declarations	Patent-holding companies announce their non-enforcement of their patents in certain regions, which allows generic suppliers to operate there without fear of legal recourse.	We cross-referenced the importing country in the generic procurement data with the corresponding originator company's policy on enforcement in that particular region	Bristol-Myers Squibb (BMS) does not enforce its patents on atazanavir (ATV) in Uganda. Uganda has granted relevant patents on ATV. Therefore, we counted BMS' non-assert policy as potentially relevant to Uganda's generic procurements of ATV.	Originator companies' non-assert declarations relevant for the ARV in question (18, 47)
Voluntary licenses (VLs)	Originator companies agree to allow generic ones to supply certain developing countries in exchange for a royalty fee.	We cross-referenced the generic procurements by countries that had granted patent protection with the countries listed in the appropriate VL agreement.	Gilead's multilateral VL with the Medicines Patent Pool on tenofovir (TDF) covers India; therefore, we counted all generic procurements of TDF bought from an Indian company as potentially relevant to the VL agreement.	The list of countries covered by the relevant originator company's VL. For bilateral agreements, we also matched the procurement data with the generic company listed in the agreement (18, 39, 47, 49-52).
Compulsory licenses (CLs)	A country has authorized a temporary bypass of a medicine patent in order to increase access to a particular drug.	We cross-referenced lists of current CLs with the ARV and importing country in the procurement data.	Indonesia recently issued a compulsory license on abacavir (ABC); therefore, we counted all of Indonesia's procurements of ABC in our dataset as potentially relevant to its CL.	Recent lists of CLs by country and product (39, 47, 53, 54)
Other	The transaction did not appear to be relevant to any of the above flexibilities.	We grouped in this category all procurement data that did not matching any of the above flexibilities on the exporting or importing side.	The Kyrgyz Republic procured lopinavir + ritonavir from Aurobindo, but this was not listed in known VLs, even though valid patents are listed there.	The product in the procurement transaction did not match with any of the lists noted above.

Table 4.8.2 – Generic procurements made within the context of patent protection corresponding to one or more of the below legal flexibilities

Explanation	TNUs	%
LDC Waiver	155,240,040	21.68%
Non-assert	2,622,894	0.37%
Voluntary licensing	562,612,618	78.56%
Compulsory licensing	1,777,980	0.25%
Other (unexplained)	151,133,574	21.10%

4.9 Figures

Figure 4.9.1 - 1.34 billion units of generic HIV medicine procurements by patent presence

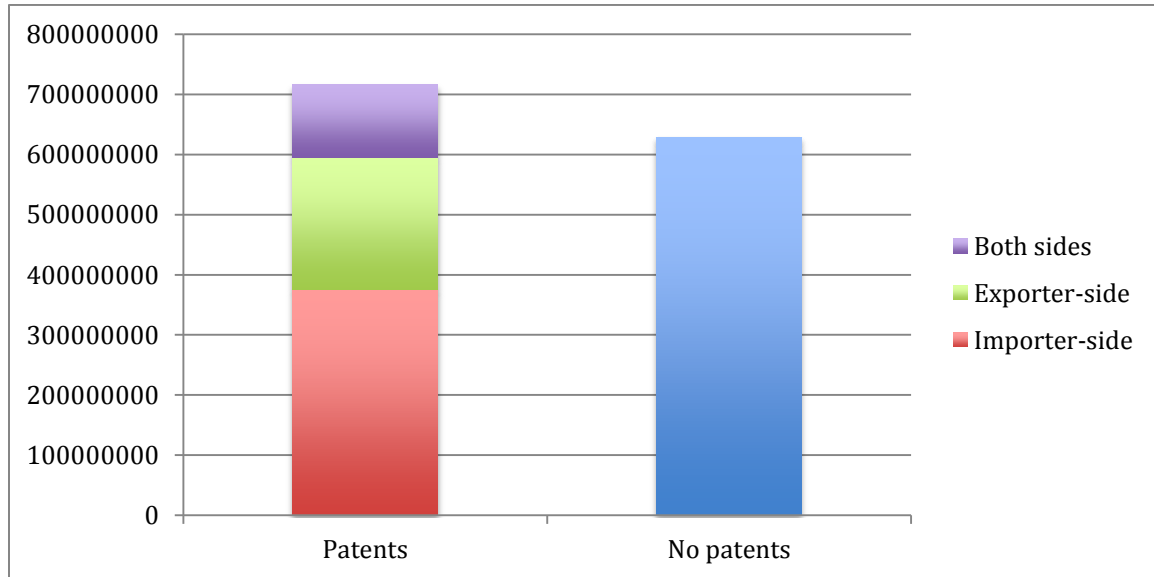


Figure 4.9.2 - Proportion of generic procurements made with(out) patent protection stratified by the importing country's level of development

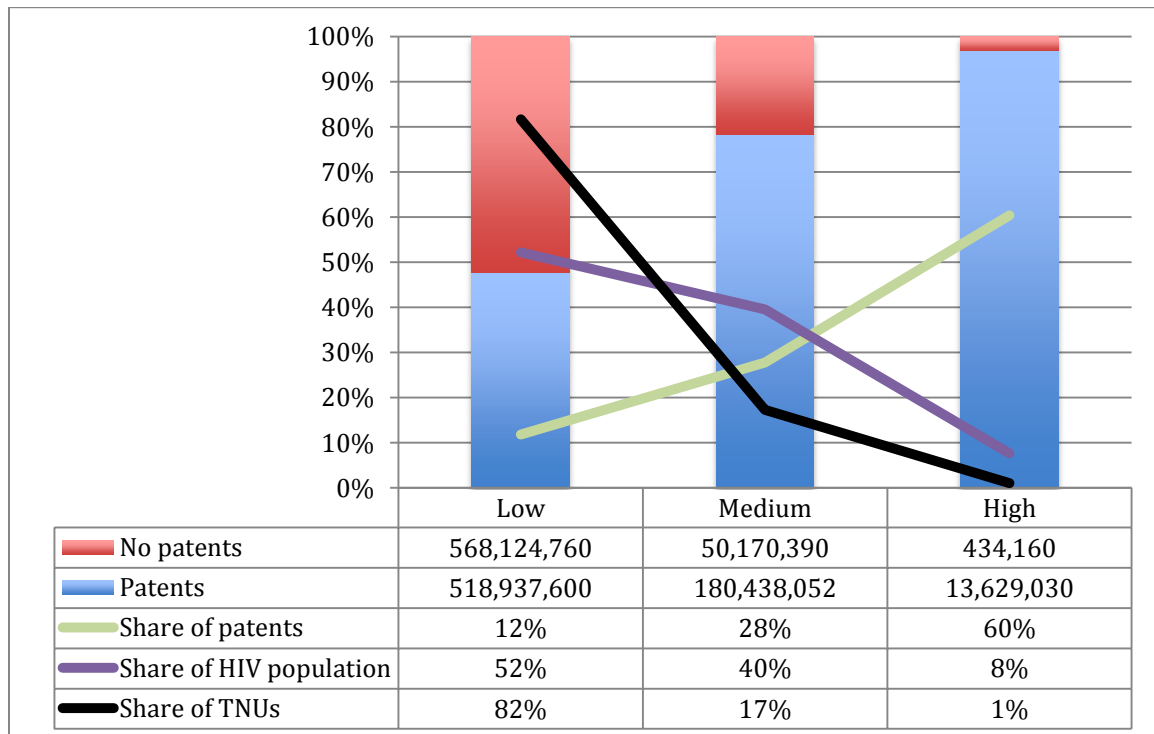
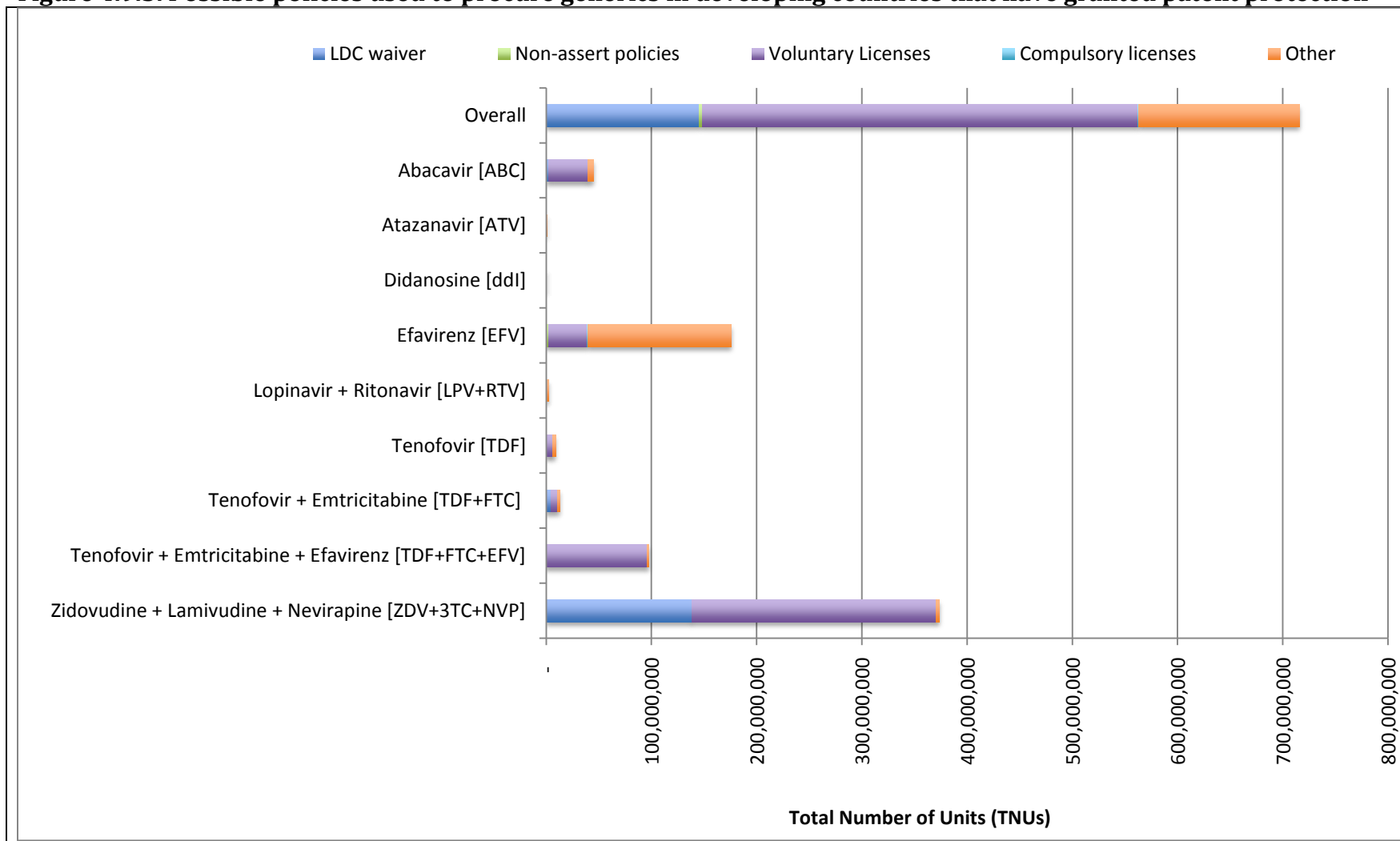
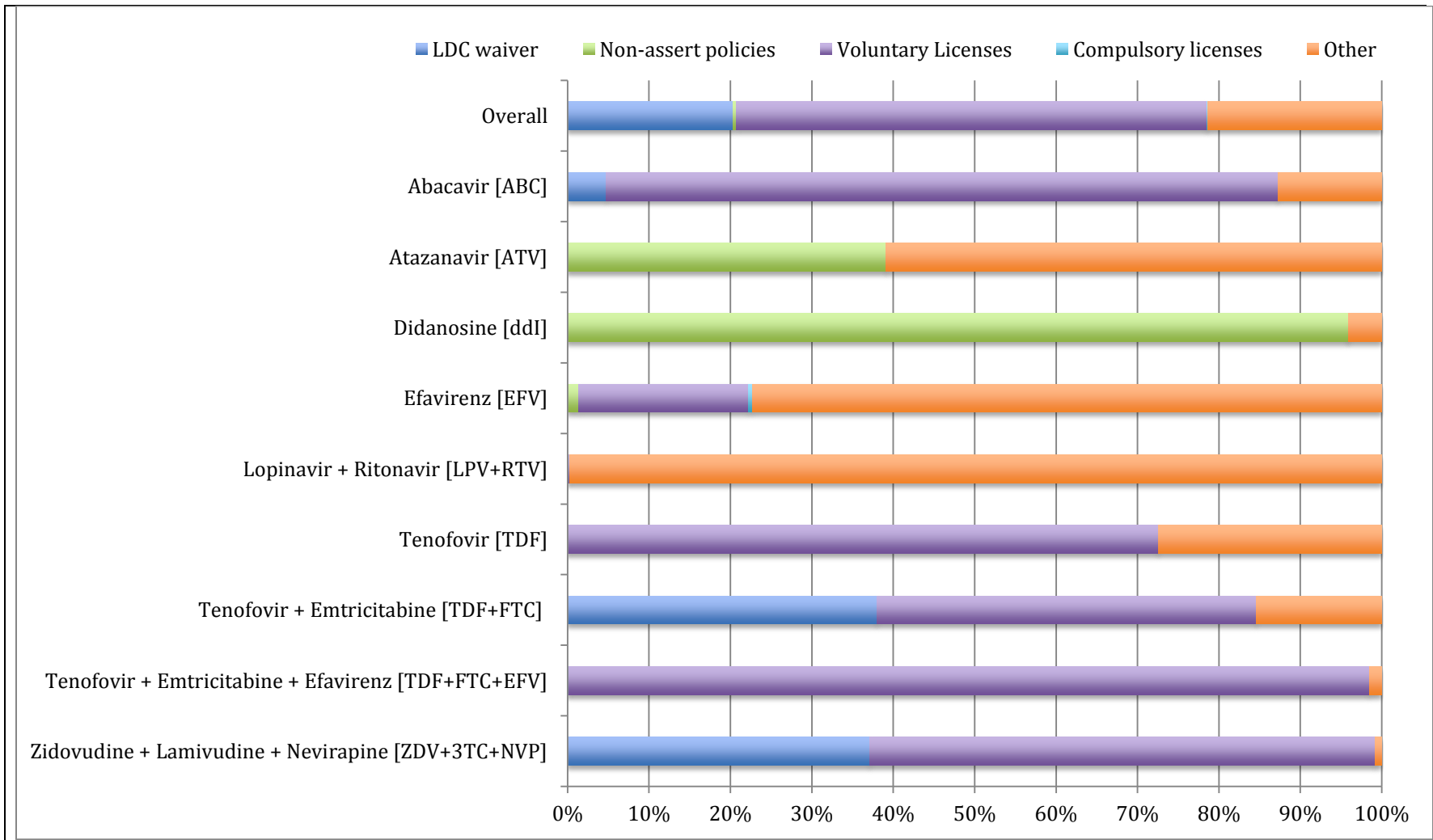


Figure 4.9.3. Possible policies used to procure generics in developing countries that have granted patent protection



Panel 1. Possible use of legal flexibilities to buy generics, stratified by products and total number of units purchased



Panel 2. Possible use of legal flexibilities shown proportionately by product

Note: We were unable to conduct this analysis for 3 of the ARVs in our sample because the only procurements captured by the GPRM for these ARVs did not correspond to any of our patent data; in other words, the only procurement data available was in the “no patents” category in Figure 1.

Chapter 5 (Article 4):
Compulsory Licenses Often Did Not Produce Lower Prices For
Antiretrovirals Compared To International Procurement Tactics

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5.1 Abstract

Compulsory licensing has been widely suggested as a legal mechanism for bypassing patents to introduce lower-cost generic antiretrovirals for HIV/AIDS in developing countries. Previous studies found that compulsory licensing can reduce procurement prices for drugs, but it is unknown how the resulting prices compare to procurements through the Global Fund to Fight AIDS, Tuberculosis, and Malaria; UNICEF; and other international channels. For this study we systematically constructed a case-study database of compulsory licensing activity for antiretrovirals and compared compulsory license prices to those in the World Health Organization's (WHO's) Global Price Reporting Mechanism and the Global Fund's Price and Quality Reporting Tool. Thirty compulsory license cases were analyzed with 673 comparable procurements from WHO and Global Fund data. Compulsory license prices exceeded the median international procurement prices in nineteen of the thirty case studies, often with a price gap of more than 25 percent. Compulsory licensing often delivered suboptimal value when compared to the alternative of international procurement, especially when used by low-income countries to manufacture medicines locally. There is an ongoing need for multilateral and charitable actors to work collectively with governments and medicine suppliers on policy options.

5.2 Introduction

The potential conflict among intellectual property protection, trade, and the need for wider access to medicines in low- and middle-income countries was recognized by policy makers during the World Trade Organization's (WTO) Uruguay Round of trade talks in the mid-1990s (1). The 1994 Agreement on the Trade-Related Aspects of Intellectual Rights (TRIPS) (2), a founding document for the WTO, required that all member states eventually provide the same level of intellectual property protection—such as twenty years of patent protection.

However, the effect of strengthening intellectual property protection in low- and middle-income countries could be to increase the prices of newer medicines and make treatment less accessible. WTO members therefore included several TRIPS flexibilities. The best known—and most controversial—of these is the “compulsory license,” which is the state-authorized licensing of generic medicines to be produced or bought without the patent owner's consent, even though this derogates from the brand-name drug's market exclusivity. The practical outcome of compulsory licensing is that buyers, including low-income countries, can legally access generic medicines before their patents expire.

The option of issuing compulsory licenses is established in international patent law. Nonetheless, actually doing so is a domestic legal matter for individual governments to decide, based on their circumstances (3).

Following the emergence of the HIV/AIDS epidemic, WTO members reaffirmed in the 2001 Doha Declaration on the TRIPS Agreement and Public Health (4) their prerogative to use compulsory licensing to improve access to antiretrovirals and other drugs. To accommodate countries that do not manufacture drugs locally, an August 30, 2003, decision of the WTO's TRIPS Council (5) gave WTO members legally binding rules on issuing

compulsory licenses for generic versions of drugs that are internationally traded (6) (so-called Paragraph 6 licenses, referring to paragraph 6 of the Doha Declaration).

Besides establishing the international legal structures for the trade of generic medicines between jurisdictions in which patents are in force, the 2003 decision and the Doha Declaration were also important for what they symbolized politically: the fact that WTO members may use TRIPS flexibilities to address domestic public health concerns.

One study (7) found that the highest level of application of compulsory licenses for antiretrovirals in developing countries was reached in the years following the 2003 decision (2003–05), but that burst of compulsory licenses subsided thereafter. Other studies showed that compulsory licenses dramatically reduce drug costs relative to the patent holder's price in a given country prior to the use of a license (8-11). For example, Martin Khor (8) reported that Thailand used compulsory licenses to save an average of 89 percent on five key drugs. However, these studies examined prices before and after the use of a compulsory license. Thus, they do not shed light on whether this strategy outperforms others for bringing cut-price drugs to developing countries.

In addition to using compulsory licenses, developing countries have worked with international programs and organizations—including the President's Emergency Plan for AIDS Relief (PEPFAR), UNICEF, Médecins sans Frontières (Doctors Without Borders), and the Clinton Foundation—to procure antiretrovirals using strategies such as collective price negotiations. Such negotiations, being voluntary, are obviously a markedly different approach compared to the licenses that, by definition, are compulsory for patent holders. Publications such as the 2012 Health Affairs special issue on PEPFAR (12) demonstrate that collective price negotiations succeed in cutting prices and improving access to treatment.

What is less well known is how the prices of medicines obtained through compulsory licensing compare to prices obtained by similar countries from international

procurement markets tracked by the World Health Organization (WHO) or the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Therefore, in this study we compared the prices that countries were able to obtain using compulsory license tactics (for example, licensing local generic manufacturing or generic imports) versus the prices that comparable countries achieved contemporaneously in international procurements.

5.3 Methods and materials

5.3.1 Phase One: Compiling A Case-Study Database

Similar to related studies that compared countries' HIV/AIDS drug procurement strategies (11, 13), our study used a multiple comparative case-study design (14, 15) (for an illustration of the study design, see Appendix 5.10.1). Compulsory license activity was documented in the same fashion as in a previous study (7). To minimize selection bias, our approach to the case-study search strategy and database construction was informed by systematic review methodologies (16-18).

To identify compulsory license case studies, we conducted searches in LexisNexis, Medline, Scopus, and Google Scholar and on state and nonstate actors' websites for the decade following the 2003 TRIPS Council decision. We checked our findings against all other known compilations of compulsory license case studies. After we completed the protocols and relevance screenings described in Appendix 5.10.1, thirty compulsory license case studies remained. Most listed price data in US dollars per unit; we converted those in other measures (such as price per patient per month or year) or other currencies using central bank exchange rates (19).

5.3.2 Phase Two: Matching International Procurement Data

To identify comparable procurements of antiretroviral drugs made on the international market, we turned to the Global Fund's Price and Quality Reporting Tool (20) and the WHO's Global Price Reporting Mechanism (21) (for a summary of these

procurements, see Appendix 5.10.2). Other scholars have used these databases to investigate international antiretroviral procurement costs and related issues (22-26).

We retrieved the price data corresponding to each compulsory licensing episode based on the following variables: drug product (irrespective of manufacturer), product strength (for example, 600 mg), calendar year of purchase, and the receiving or buying nation's Human Development Index category (low, medium, high, or very high) (27). Focusing on "peer countries" in the same Human Development Index category as the country of a compulsory license case study helped us control for variations that could affect procurement tactics, such as income and overall country development status, and gave us more conservative findings than would have otherwise been the case.

After we used these variables to filter the data, 673 procurement entries from the Global Fund's Price and Quality Reporting Tool (n=74) and the WHO's Global Price Reporting Mechanism (n=599) from eighty-six countries remained. We grouped these entries into thirty subsets, each corresponding to a compulsory license case study, and we calculated each subset's median drug price per unit (for these prices, see the Appendix 5.10.2).

5.3.3 Phase Three: Comparing Prices

We matched each compulsory license case study price to the corresponding median international procurement price given to peer countries in the same Human Development Index category in the same year. Next, we analyzed the relative price difference as a ratio, with 1 signifying perfect price equivalence, less than 1 reflecting a cheaper compulsory license price, and greater than 1 indicating a cheaper international procurement price. We report here the magnitude of these thirty ratios, the frequency with which the compulsory license or international procurement price outperformed the other, and the frequency with which there was a price difference of more than 25 percent.

Finally, we performed robustness tests by reanalyzing the overall outcomes using the matched international procurements mean, weighted mean by purchase volume, and minimum price instead of the median price. In addition, we stratified the comparisons into subsets according to factors that we suspected might affect the results (for example, using only the comparisons that involved compulsory licenses for local manufacturing).

5.3.4 Limitations

A limitation of our analytical approach is that because the necessary data do not exist, we could not account for specific cost drivers (such as delivery costs, insurance, and taxes) or variations within either the compulsory licensing or international procurement strategy, even though these can affect medicine prices. However, we drew conclusions based on comparisons in which the observed price difference was more than 25 percent. Thus, these and other unknown or unobserved factors are unlikely to alter the overall results.

5.4 Results

The overall median of the thirty price ratios (1.48) favoured international procurement (Table 5.8.1). However, several price points were nearly the same, and results often showed a range that straddled the line of equivalence. The compulsory licensing price was higher than the international procurement price in nineteen of the thirty comparisons (63 percent).

The same basic result was found when a price difference threshold of 25 percent was applied to signal substantial cost disadvantages. In this analysis there remained seventeen of the thirty cases (57 percent) in which the compulsory licensing price was higher than the international procurement price and only five of the thirty cases (17 percent of the comparisons) where it was lower. Furthermore, this pattern held when we used the

mean (1.34) or weighted mean (1.33) prices instead of the median procurement price for peer countries.

In the most extreme case, when we used the minimum price attained by any peer country (matched according to the Human Development Index category) buying contemporaneously, the international procurement price was lower in twenty-six of the thirty comparisons (87 percent). In this case, the compulsory license/international price ratio was more than double (2.02).

Figure 5.9.2 displays the price ratio data chronologically by drugs and compulsory licensing country, logarithmically relative to peer countries matched according to the Human Development Index, and stratified by the type of license application. Notably, when we restricted comparisons to cases of compulsory licenses for local production, the median price ratio was 1.83 (Table 5.8.1). No case had a compulsory licensing price that was more than 25 percent cheaper, and nine of eleven cases had an international procurement price that was more than 25 percent cheaper (Table 5.8.1). The latter finding overwhelmingly shows that countries using compulsory licenses for local production overpaid for medicines relative to peer countries in the same Human Development Index category using international procurement.

When we restricted comparisons to compulsory licenses used for generic importation, the median price ratio shifted to 0.90 in favour of the compulsory licensing price (Table 5.8.1). Yet that price was more than 25 percent lower in four cases, and the international procurement price was more than 25 percent lower in the same number of cases. This equivalency suggests that this kind of compulsory license—that is, a license used for importing a generic drug—has historically produced a substantial cost advantage relative to international procurement channels as often as it has done the opposite.

Table 5.8.1 also shows the results of robustness tests in which we stratified the thirty comparisons into subsets to control for potential confounders. The disadvantage of the compulsory licensing price persisted even in the following cases: restricting the comparisons to those with ten or more international procurements among peers; excluding licenses issued in 2003, when the international procurement data were sparse; excluding cases in Thailand, Brazil, or both (the countries that were the two most active issuers of licenses) in case they had disproportionate influence on the data; and separating countries that were better off from those that were worse off (countries with a Human Development Index categorization of medium or low development, respectively).

We reasoned that better-off countries might have been at a disadvantage in the international procurement market because of drug manufacturers' reluctance to sell to them at a discount—which in turn might have driven them to rely on compulsory licensing. Sample sizes were small. However, we found that better-off countries still paid more when using compulsory licensing than when using international procurement: Table 5.8.1 shows a price ratio of 1.21 for these twenty-three comparisons.

These countries, however, were more successful at closing the gap between the two prices than were countries at a lower level of development: The worse-off countries' price ratio was 1.83. Out of seven comparisons with compulsory licensing in the worse-off countries, only one resulted in a lower price than the international procurement price. In the other six cases, compulsory licensing prices were more than 25 percent higher.

Only two sensitivity tests brought compulsory licensing and international procurement prices to near equivalence. First, we considered that patenting in peer countries might influence international procurement prices and therefore the validity of that control group. We recalculated median international procurement prices using only the data for peer countries in which any of three patent landscape studies (28-30) observed

patent protection for the product in question (for a summary of these procurements and prices, see the Appendix 5.10.3). This reduced the comparisons to twenty-one case studies, primarily by excluding less developed countries, in which patenting is not prevalent. It also reduced the number of international procurements available for comparison, because generic procurements were less common (although not absent) where patents exist.

This restriction increased the median international procurement price, so that the compulsory licensing price was cheaper in twelve of the twenty-one cases (57 percent), and the median price ratio was 0.83 (Table 5.8.1). Compulsory licensing modestly outperformed international procurement in this test. However, that performance was not reliable, since there were eight cases in which the compulsory license price bested the international procurement price by more than 25 percent and another eight cases in which the reverse was true.

Second, to account for the possibility that compulsory licensing activity in a given calendar year drove down contemporaneous international procurement prices, we compared compulsory licensing prices to international procurement prices in the previous calendar year. In this test, the two prices were virtually tied (the price ratio was 0.97), with neither reliably outperforming the other.

This virtual tie in a deliberately mismatched comparison is best interpreted as validating the hypothesis that compulsory licensing prices are generally higher than international procurement prices. The analysis necessarily overlooked the fact that there has been a secular downward trend in antiretroviral prices each year for the past decade (31). Without this effect, the compulsory licensing price would be markedly higher, as our base analysis shows.

5.5 Discussion

Our study used a case-matching methodology to show that the use of compulsory licenses for antiretrovirals resulted in prices that were generally higher than the prices achieved by peer countries that bought the drugs from international procurement markets tracked by the WHO or the Global Fund in the same year. Relative to the prices reported before compulsory licensing was implemented (for these prices, see the Appendix 5.10.2), the median cost savings of changing to a compulsory licensing strategy was 71 percent. In contrast, peer countries that chose the international procurement strategy saved 79 percent. In most of our sensitivity tests, international procurement outperformed compulsory licensing, usually with a price savings of more than 25 percent.

Furthermore, compulsory licenses issued by countries to manufacture medicines locally resulted in the most overpriced medicines, relative to the alternative of international procurement (the price ratio was 1.83). In this set of eleven cases, only two instances (both were in Ecuador in 2010) had a compulsory licensing price that was lower than the international procurement price, and in none of the eleven cases was the licensing price more than 25 percent lower.

Countries may desire a compulsory licensing strategy as a possible way to build a local pharmaceutical industry, even if it means overpaying for drugs. However, the ethics of this kind of policy are thorny, since this means that, given a fixed budget, fewer antiretrovirals will be bought and fewer HIV/AIDS patients will be treated.

The compulsory licensing price disadvantage was worst for those countries that were less well off in terms of Human Development Index score—the very countries that most need to save money. This finding is striking, considering the calls for poor nations to increase their use of compulsory licensing (32, 33). The available evidence is that this strategy is not in the best interest of countries with low development, when international

procurement has been available as an alternative. The relatively low number of compulsory licenses from such countries also doubtless reflects the fact that there are few medicine patents in those countries (28, 29).

This study should not be interpreted as ideologically opposing compulsory licensing. Indeed, we documented several instances in which compulsory licensing was comparable to international procurement, especially in some of the alternate matching scenarios, such as those in which the comparison data only came from comparable developing countries that had also granted patents on the medicine in question. Our study does not preclude the possibility that compulsory licenses can be advantageous under certain circumstances and that these licenses have indirectly contributed to lowering international prices. Furthermore, the existence of compulsory licensing as a legal right likely exerts a generalized downward pressure on global medicine prices, much as the legal right of industrial action (such as strikes and lockouts) exerts pressure on labour prices. Instead, our study's results should be seen merely as furnishing evidence that in the past decade, other strategies are capable of delivering prices that are comparable or even better than compulsory licensing and should be amongst the policy options considered.

It also appears that using a wide, synergistic repertoire of cost containment strategies, including both compulsory licensing and international procurement, could be optimal. A good example, summarized by Nathan Ford and colleagues, is Thailand's deft merging of strategies for lopinavir plus ritonavir (Kaletra) (11). In August 2006, following negotiations with Thailand, Abbott Laboratories (the supplier of the brand-name drug) announced discounted pricing of \$2,200 per patient per year. Dissatisfied, Thailand announced a compulsory license in January 2007 to manufacture the medicine locally. However, a month later an Indian generic manufacturer offered a price of \$1,333 per patient per year. Abbott counter-offered \$1,000 per patient per year. In May 2007 the

Clinton Foundation facilitated a pooled procurement deal between Indian generics firms and sixty-five countries, with a price of \$676 per patient per year (US\$0.463 per unit). The best price was achieved after multiple strategies (bargaining, tiered pricing, pooled procurement, compulsory licensing, and so on) were used, not just one of them.

Our study covered a time period in which Indian generic firms competed in the antiretroviral market and heavily influenced prevailing international prices. However, such influence is less likely to be exerted today than it was in the past, because of the transition in India and elsewhere toward TRIPS compliance and medicine product patentability (a type of patent protection that India previously did not award) in 2005 (34). The full effects of this change with respect to new medicines have yet to be fully felt because many of the antiretrovirals sought after in the international market predate this transition, are already available as generics, and remain effective treatments.

If this change eventually causes a reduction in the supply of generic alternatives to patented medicines, as would be expected, the affordability of medicines in international procurement could be limited. Averting this outcome, especially as the global burden of treatable communicable diseases (such as hepatitis C) and noncommunicable diseases (such as cancer, hypertension, and diabetes) is rising, requires thoughtful policy attention from the international community.

5.5.1 Policy implications

In a future that requires all WTO countries to fully comply with TRIPS, generic firms wishing to export their versions of patented medicines into the international procurement market will require one of two strategies: either so-called Paragraph 6 compulsory licenses, or voluntary out-licenses from the patent holders—that is, licenses to one or more generic firms to supply specified developing markets with a medicine in exchange for royalties, which are generally low or waived. We discuss both briefly.

Under the Paragraph 6 System, medicine-producing WTO members can issue compulsory licenses strictly for manufacturing and exporting medicines to medicine-consuming WTO members (the consuming states may also need to issue a corresponding compulsory license for importation, depending on a given drug's patent status there). This strategy has been used only once, when Canada issued a compulsory license to a Canadian drug manufacturer (Apotex) that supplied medicines to Rwanda.

On that occasion, the system failed to deliver the lowest prices, given the availability of Indian generic alternatives through international procurement. For example, Apotex's initial quote on an antiretroviral coformulation (lamivudine plus nevirapine plus zidovudine) of US\$0.390 per unit in 2007 (35) far exceeded Rwanda's contemporaneous prices for Indian generic procurements of US\$0.191 and US\$0.303 per unit (21).

Not wanting to lose the sale, Apotex halved its price the following year and sold the drug at US\$0.195 per unit (35). That was of negligible benefit to Rwanda, since the country also bought the drug contemporaneously from Indian companies for US\$0.198–US\$0.210 per unit (21). Thus, the Paragraph 6 System proved tractable in this case, but it also had little public health impact. Apotex's compulsory license pricing struggled to catch up with international procurement pricing, not the other way around.

Were the situation reversed, the Paragraph 6 System could be useful. Perhaps if the Indian or other foreign companies had been competing under a Paragraph 6 authorization, as Canada's Apotex was, a competitive dynamic could have been sustained. However, that has not happened since the Paragraph 6 System was enacted in 2003.

Voluntary out-licenses have been a more successful way to provide access to drugs at reasonable prices. In this alternative to compulsory licensing, outlined by Michael Friedman and coauthors in 2003 (36), patent holders allow both their patents and their non-patent know-how to be used by selected generic manufacturers, who undertake to

supply the medical needs of selected countries or markets. Gilead Sciences recently chose the out-licensing strategy to expand access to sofosbuvir and ledipasvir for hepatitis C. Specifically, it authorized seven Indian generic firms to manufacture and export generic products to ninety-one countries, in exchange for a royalty of 7 percent (37).

This out-licensing not only maintained a competitive market for international procurement by those countries, but it also was especially advantageous to India because the terms included the transfer of Gilead's know-how (that is, its technology) as well as the patent—a clear advantage over compulsory licensing (38).

Critics object that out-licensing excludes certain middle-income countries, such as Mexico and countries in Eastern Europe (39). However, a greater error would be to lump reasonably developed countries under the same out-licensing terms as those afforded the least developed countries (for example, Haiti and Sierra Leone), where the ability to negotiate procurement terms—or even afford medicines—is not comparable.

Notwithstanding that sort of disagreement about where to draw the line, voluntary out-licensing has greatly outperformed Paragraph 6 compulsory licensing in providing access to medicines, whether measured by products, countries, diseases, or patients (40). Whether that remains true in the future will depend on patent holders' willingness to grant voluntary out-licenses on equitable terms and on the actualization of those agreements (41).

5.6 Conclusion

The rise of non-communicable illnesses that are treated with novel medicines, and the concomitant effect of TRIPS-compliant medicine product patentability, will undoubtedly demand strategies for access to drugs in low- and middle-income countries that are more comprehensive, proactive, flexible, and imaginative than have been common in the

HIV/AIDS era. Nonetheless, recent experience with strategies to improve access to drugs in the HIV/AIDS era remains instructive.

We found that in the past decade, using compulsory licensing tactics generally resulted in drug prices that were higher than the prices achieved by peer countries buying from international procurement markets tracked by the WHO or the Global Fund. This evidence suggests that other strategies should be given proper consideration before assuming that compulsory licensing will always yield the best possible results, especially if those licenses are to authorize the local manufacturing of medicines in low-income settings.

To be clear, there are indeed some circumstances that may warrant compulsory licenses. We foresee an ongoing though limited role for compulsory licensing in the future. We also foresee the potential for the use of Paragraph 6 compulsory licenses to increase. Nonetheless, we believe that voluntary out-licensing, such as Gilead Science's recent agreements, holds great promise as these arrangements produced some of the lowest prices while still facilitating technology transfer (including patent and non-patent know-how) to generic manufacturers based in developing countries.

Balancing these policy options is complex. That fact makes it all the more important for governments to make medicine procurement choices through transparent, collaborative processes in which governments and multilateral and charitable actors work in a collective or pooled fashion with medicine suppliers. As the global disease burden shifts toward illnesses that can be treated with novel medicines, this sort of approach is likely to come closest to the shared goal of equitable access.

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5.8 Tables

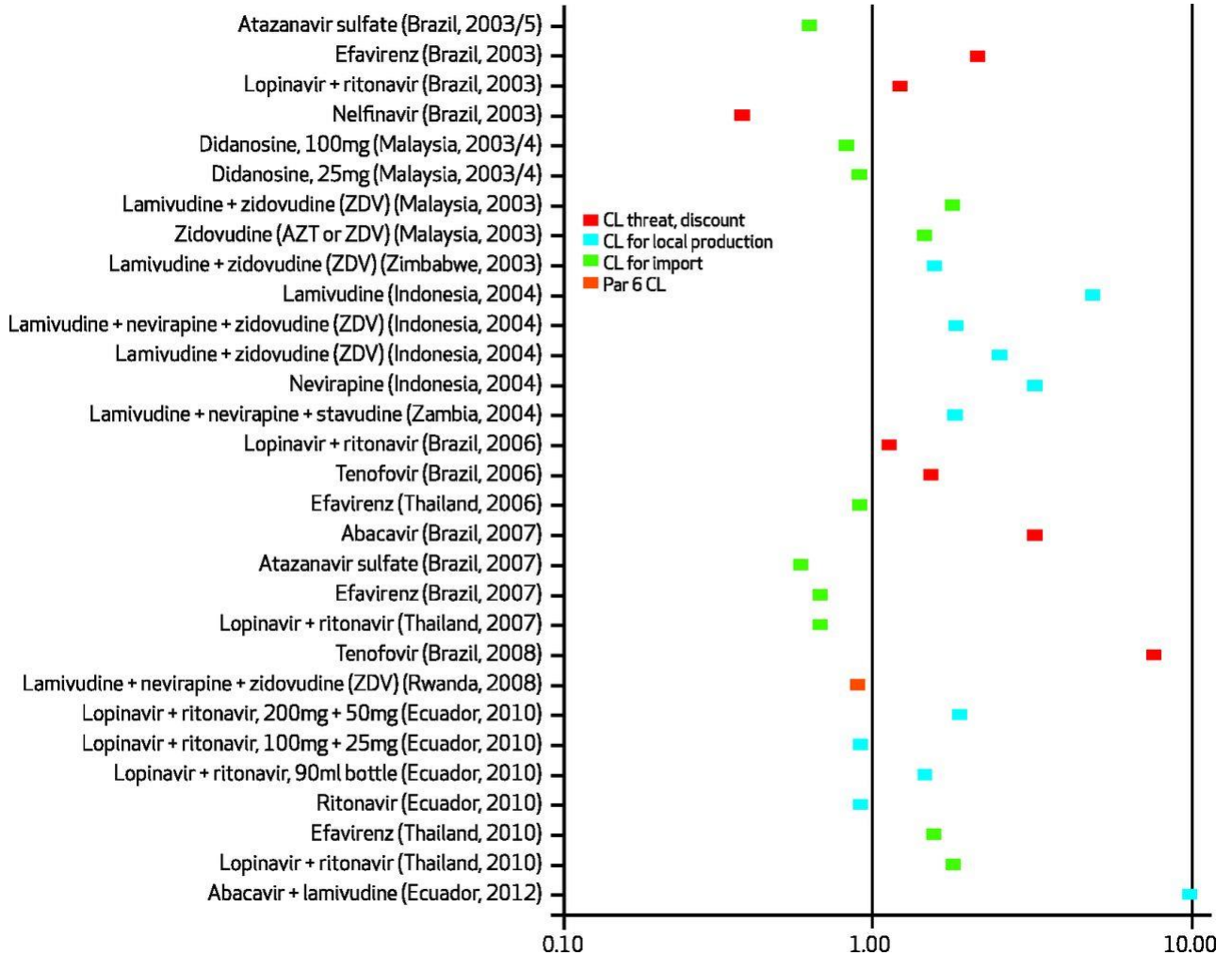
Table 5.8.1 Prices of drugs purchased through compulsory license and international procurement mechanisms

Test	Number of possible comparisons	Median ratio of comparisons, CL/Int'l	Number of cases in which:			
			CL cheaper than Int'l	Int'l cheaper than CL	CL cheaper by >25%	Int'l cheaper by >25%
<i>Overall results</i>						
Median procurement price	30	1.48	11	19	5	17
Mean procurement price	30	1.34	11	19	5	15
Weighted mean procurement price	30	1.33	9	21	5	14
Minimum procurement price	30	2.02	4	26	3	14
<i>Stratification of the case studies by potential confounders</i>						
Cases of CLs for local production only	11	1.83	2	9	0	9
Cases of CLs for import only (including Paragraph 6 CLs)	12	0.90	8	4	4	4
Cases with more than 10 or more int'ls among peers	12	1.67	5	7	2	7
Excluding 2003 comparisons	21	1.56	7	14	3	13
Excluding Brazil case studies	20	1.49	7	13	1	13
Excluding Thailand case studies	26	1.48	9	17	4	15
Excluding Thailand and Brazil	16	1.67	5	11	0	11
Countries with medium HDI	23	1.21	10	13	5	11
Countries with low HDI	7	1.83	1	6	0	6
Match only to peers where product is patented	21	0.83	12	9	8	8
Match to int'ls in previous year	18	0.97	9	9	5	7

SOURCE/NOTES: Authors' analysis of the price data from the case study database (see the Appendix for a complete list of references) matched against the data contained in note 21 and 22 according to the criteria described in the methods section. NOTES Paragraph 6 compulsory licenses (CLs) are explained in the text. Int'l is international procurement. HDI is Human Development Index. Medium HDI countries were relatively more developed (scoring above 0.6) than low HDI countries (scoring below 0.6).

5.9 Figures

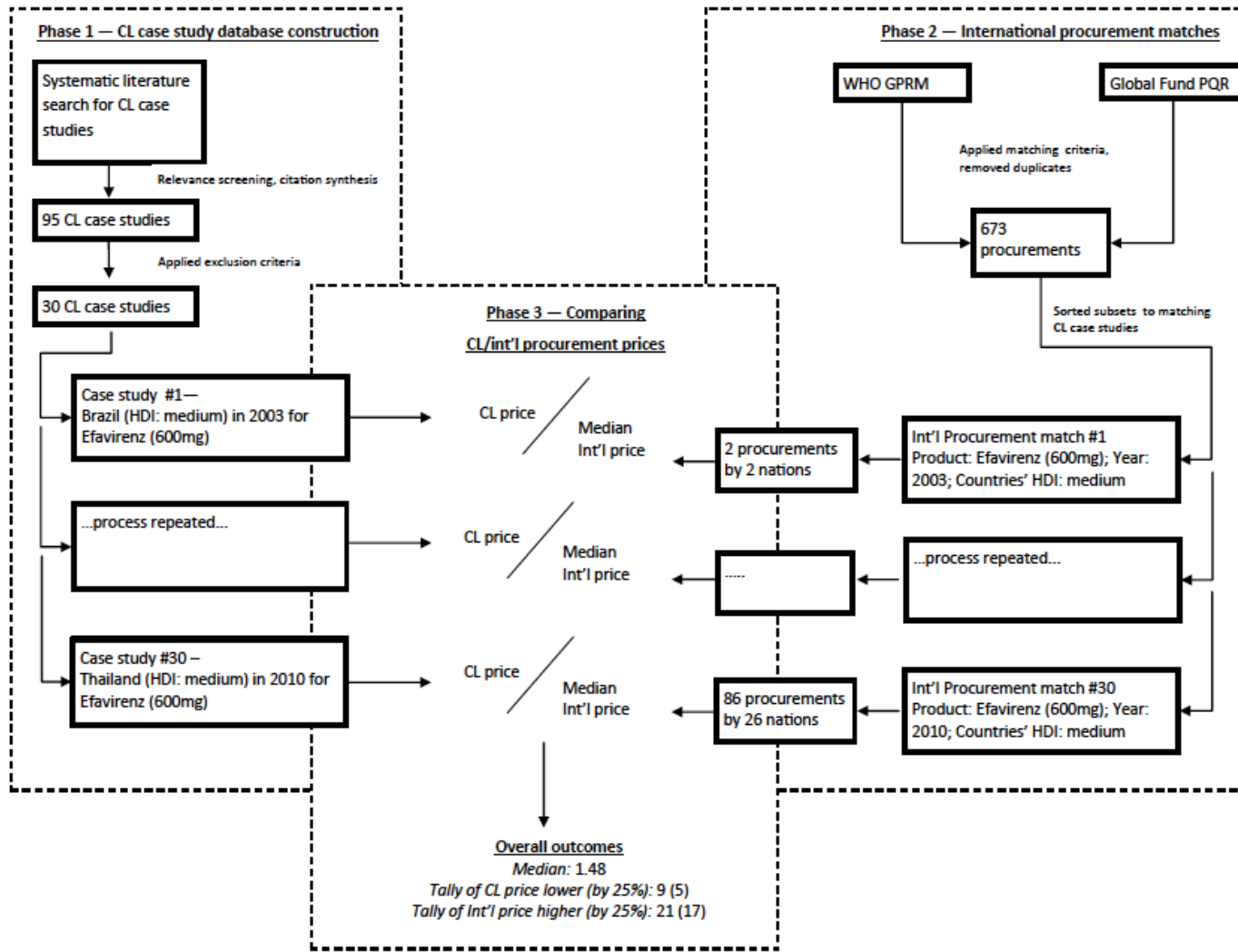
5.9.1 Ratios of compulsory licensing (CL) to international procurement prices for antiretroviral drugs



Source/Notes: Authors' analysis of the price data from the case study database (see the Appendix for a complete list of references) matched against the data contained in note 21 and 22 according to the criteria described in the methods section. NOTES "Compulsory license (CL) threats for discounts" were used to exert price negotiating pressure on patent-holding drug companies but were not carried out because a price agreement was reached. When we excluded these threats, the median price ratio was 1.44. See Exhibit 1 for results focusing on the other three CL types: "CLs for local production" (which authorize domestic generic manufacturing of a drug), "CLs for import" (which authorize the importation of a generic drug from a foreign country where the drug is not patented), and "Par 6 CL" (which involves the use of the Paragraph 6 system—explained in the text—and authorizes the importation of a generic drug from a foreign country where the drug is patented and where corresponding CLs are issued).

5.10 Appendices

Appendix 5.10.1 Three phase approach to CL case study to international procurement price comparison study



Appendix 5.10.2 – CL case study price compared to international procurement for peer countries

Note: Our methodological approach to populating our case study database began with wildcard searches in LexisNexis with (pharma! OR drug!) AND (compulsory licen!) within the proximity (W/99) of the name of any WTO member state in any form (e.g., Albania!). The search covered over 45,000 sources of academic, legal, and grey literature (e.g., industry reports, quarterly reports by pharmaceutical firms, news media) reporting actual or threatened CLs. As the ARV procurement and pricing data described in the second phase of this investigation begins in 2003, our literature search was limited to the previous decade and was run on August 30, 2013 (the decade anniversary of the August 30, 2003 Decision), yielding 2,242 documents, of which 151 articles were relevant and coded by case in an EndNote database. The literature type of pricing data was noted. This database was crosschecked against all other known compilations of CL case studies (n=14) (1-14). To ensure saturation, supplemental searches were performed on Medline, Scopus, Google Scholar, websites of non-state actors (e.g., IP Watch, Knowledge Ecology International), archival editions of MSF's "Untangling the web of antiretroviral price reductions" publications (15), and websites of international organizations (e.g., WTO, WHO, WIPO) and public authorities. While these supplementary searches were useful for gathering additional information, these efforts did not identify any new case studies. The following inclusion criteria were then applied: the cases implicated one or more ARVs (resulting in 44 exclusions for other diseases); were government-led as is legally required to initiate compulsory licensing (10 exclusions for NGO-led efforts that elicited no state action); involved a WTO member state (1 exclusion for Eritrea); resulted in a published price point for comparison (10 exclusions where governments in Mozambique and Indonesia announced intent for CL but did not provide a price estimate as production had not begun); and were for a specific product rather than a categorical CL for all ARVs (3 exclusions, as specific products and prices are needed to make comparisons).

Product	Year	Nation	Pre-CL	Post-CL	Int'l price median (min, max)	# procurements (# peer nations)	% int'l prices generic	CL-to-Int'l ratio	Lower price	Ref. & source type
Abacavir 300mg	2007	Brazil	\$2.67	\$2.00	\$0.62 (0.52 - 4.84)	13 (6)	77%	3.24	Int'l	(16) ⊗
Abacavir+Lamivudine 600mg+300mg	2012	Ecuador	\$25.10	\$6.28	\$0.62	1	100%	10.07	Int'l	(17, 18) ♥
Atazanavir sulfate 150mg	2003 (Int'l 2005)*	Brazil	\$13.80	\$3.25	\$5.14 (\$5.07 - 5.21)	2 (1)	50%	0.63	CL	(8, 19) ♠
Atazanavir sulfate 150 mg	2007	Brazil	\$3.29	\$3.07	\$5.25 (5.00 - 5.50)	2 (2)	0%	0.58	CL	(8, 20) ♠
Didanosine 100mg	2003 (Int'l 2004)*	Malaysia	\$2.12	\$0.33	\$0.40 (0.18 - 0.78)	8 (3)	50%	0.82	CL	(21) ♣
Didanosine 25mg	2003 (Int'l 2004)*	Malaysia	\$0.74	\$0.10	\$0.11	1	100%	0.91	CL	(21) ♣
Efavirenz 600mg	2003	Brazil	\$7.71	\$2.08	\$0.97 (0.95 - 1.00)	2 (2)	0%	2.14	Int'l	(3) ♦
Efavirenz 600mg	2006	Thailand	\$1.37	\$0.73	\$0.80 (0.29 - 2.60)	75 (23)	51%	0.92	CL	(4) ♦

Product	Year	Nation	Pre-CL	Post-CL	Int'l price median (min, max)	# procurements (# peer nations)	% int'l prices generic	CL-to-Int'l ratio	Lower price	Ref. & source type
Efavirenz 600mg	2007	Brazil	\$1.59	\$0.45	\$0.67 (0.38 - 5.00)	54 (20)	65%	0.68	CL	(2, 4) ♦
Efavirenz 600mg	2010	Thailand	\$1.40	\$0.29	\$0.19 (0.14 - 2.12)	86 (26)	79%	1.56	Int'l	(8, 22, 23) ♥
Lamivudine 600mg	2004	Indonesia	\$5.17	\$0.47	\$0.10 (0.08 - 0.18)	17 (7)	24%	4.91	Int'l	(2) ♥
Lamivudine+Nevirapine+Stavudine 150mg+200mg+40mg	2004	Zambia	No data	\$0.41	\$0.23 (0.18 - 0.49)	29 (11)	100%	1.83	Int'l	(24, 25) ♠
Lamivudine+Nevirapine+Zidovudine 150mg+200mg+300mg	2004	Indonesia	\$10.00	\$0.63	\$0.35	1	0%	1.81	Int'l	(2, 26) ♥
Lamivudine+Nevirapine+Zidovudine 150mg+200mg+300mg	2008	Rwanda	\$20.00	\$0.20	\$0.22 (0.17 - 0.34)	114 (18)	100%	0.88	CL	(27-29) ♦
Lamivudine+Zidovudine 150mg+300mg	2004	Indonesia	\$6.67	\$0.81	\$0.32 (0.22 - 3.69)	37 (18)	54%	2.51	Int'l	(2) ♥
Lamivudine+Zidovudine 150mg+300mg	2003	Malaysia	\$4.77	\$0.67	\$0.38 (0.38 - 0.43)	3 (1)	100%	1.80	Int'l	(21) ♣
Lamivudine+Zidovudine 150mg+300mg	2003	Zimbabwe	\$0.59	\$0.49	\$0.32 (0.18 - 0.51)	5 (5)	40%	1.54	Int'l	(1, 4) ♦
Lopinavir+Ritonavir 133.3mg + 33.3mg	2003	Brazil	\$5.05	\$2.22	\$1.83 (1.83 - 1.84)	2 (1)	0%	1.21	Int'l	(3, 30) ♦
Lopinavir+Ritonavir 200mg+50mg	2006	Brazil	\$1.17	\$0.63	\$0.56	1	0%	1.13	Int'l	(2, 31) ♥
Lopinavir+Ritonavir 200mg+50mg	2007	Thailand	\$1.51	\$0.46	\$0.68 (0.34 - 0.83)	24 (10)	4%	0.68	CL	(3) ♦
Lopinavir+Ritonavir 200mg+50mg	2010	Ecuador	\$0.78	\$0.57	\$0.31 (0.28 - 0.89)	84 (23)	69%	1.85	Int'l	(8, 32, 33) ♣
Lopinavir+Ritonavir 100mg+25mg	2010	Ecuador	No data	\$0.32	\$0.35 (0.16 - 0.44)	7 (3)	57%	0.90	CL	(33) ♣
Lopinavir+Ritonavir 80mg+20mg (90ml bottle)	2010	Ecuador	No data	\$24.0	\$16.77 (7.23 - 44.20)	14 (7)	0%	1.43	Int'l	(33) ♣
Lopinavir+Ritonavir 200mg+50mg	2010	Thailand	No data	\$0.54	\$0.31 (0.28 - 0.89)	84 (23)	69%	1.77	Int'l	(22) ♥

Product	Year	Nation	Pre-CL	Post-CL	Int'l price median (min, max)	# procurements (# peer nations)	% int'l prices generic	CL-to-Int'l ratio	Lower price	Ref. & source type
Nelfinavir 250mg	2003	Brazil	\$0.83	\$0.52	\$1.36	1	0%	0.39	CL	(2, 7) ♥
Nevirapine 200mg	2004	Indonesia	\$1.60	\$0.47	\$0.14 (0.02 - 0.70)	31 (15)	68%	3.26	Int'l	(2) ♥
Ritonavir 100mg	2010	Ecuador	\$1.34	\$0.98	\$1.09 (0.11 - 2.21)	16 (11)	0%	0.90	CL	(8, 33) ♣
Tenofovir 300mg	2006	Brazil	\$7.58	\$3.78	\$2.50 (0.57 - 4.90)	9 (7)	0%	1.51	Int'l	(34, 35) ♥
Tenofovir 300mg	2008	Brazil	\$6.85	\$3.80	\$0.51 (0.41 - 1.28)	32 (14)	63%	7.50	Int'l	(36) ♦
Zidovudine 100mg	2003	Malaysia	\$0.78	\$0.16	\$0.11	1	100%	1.44	Int'l	(21) ♣

* International data unavailable in same year as CL (which favours the international procurement price as it falls each year, yet the CL price was still lower); the soonest available data is used here.

CL price source's literature type: ♣price listed on CL; ♦academic; ♥civil society; ♠industry publications; ☒news media

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Appendix 5.10.3 – CL case study price compared to international procurement stratified by product’s patent status in peer country comparators

Note: The final column notes the number of procurements for which none of the patent landscape studies noted in the manuscript had investigated patent status; therefore, these procurement prices were excluded for the sensitivity test described in the Results section.

Product	Year	Nation	Post-CL	Patented in peer nation – median int’l price (min – max)	Patented in peer nation – # procurements (# nations)	Lower median (min) price	Not patented in peer nation – int’l median price (min – max)	Not patented in peer nation – # procurements (# nations)	Lower median (min) price	# buys where patent status not known
Abacavir 300mg	2007	Brazil	\$2.00	\$4.84	1	CL	\$0.68 (0.52 – 0.93)	8 (4)	Int’l	4
Abacavir+Lamivudine 600mg+300mg	2012	Ecuador	\$6.28	\$0.62	1	Int’l	no data	-	-	0
Atazanavir sulfate 150mg	2003 (Int’l 2005)*	Brazil	\$3.25	\$5.14 (5.07– 5.21)	2 (1)	CL (CL)	no data	-	-	0
Atazanavir sulfate 150 mg	2007	Brazil	\$3.07	\$5.50	1	CL	\$5.00	1	CL	0
Didanosine 100mg	2003 (Int’l 2004)*	Malaysia	\$0.33	\$0.40 (0.40 – 0.40)	4 (1)	CL	\$0.18 (0.18 – 0.78)	3 (1)	Int’l	1
Didanosine 25mg	2003 (Int’l 2004)*	Malaysia	\$0.10	no data	-	-	no data	-	-	1
Efavirenz 600mg	2003	Brazil	\$2.08	\$0.95	1	Int’l	\$1.00	1	Int’l	0
Efavirenz 600mg	2006	Thailand	\$0.73	\$0.77 (0.53 – 2.05)	29 (5)	CL (Int’l)	\$0.83 (0.29 – 2.60)	28 (11)	CL	18
Efavirenz 600mg	2007	Brazil	\$0.45	\$1.58 (0.40 – 5.00)	3 (3)	CL (Int’l)	\$0.55 (0.38 – 1.91)	23 (9)	CL (Int’l)	28

Product	Year	Nation	Post-CL	Patented in peer nation – median int'l price (min – max)	Patented in peer nation – # procurements (# nations)	Lower median (min) price	Not patented in peer nation – int'l median price (min – max)	Not patented in peer nation – # procurements (# nations)	Lower median (min) price	# buys where patent status not known
Efavirenz 600mg	2010	Thailand	\$0.29	\$0.65 (0.15 – 1.15)	23 (4)	CL (Int'l)	\$0.18 (0.14 – 0.40)	44 (14)	Int'l	19
Lamivudine 600mg	2004	Indonesia	\$0.47	\$0.10 (0.08 -0.18)	12 (4)	Int'l	\$0.09	1	Int'l	4
Lamivudine+Nevirapine+Stavudine 150mg+200mg+40mg	2004	Zambia	\$0.41	\$0.22 (0.19 – 0.30)	3 (3)	Int'l	\$0.22 (0.18 - 0.49)	14 (4)	Int'l	12
Lamivudine+Nevirapine+Zidovudine 150mg+200mg+300mg	2004	Indonesia	\$0.63	no data	-	-	\$0.35	1	Int'l	0
Lamivudine+Nevirapine+Zidovudine 150mg+200mg+300mg	2008	Rwanda	\$0.20	\$0.24 (0.18 – 0.34)	64 (10)	CL (Int'l)	\$0.20 (0.17 - 0.35)	47 (6)	Tie (Int'l)	3
Lamivudine+Zidovudine 150mg+300mg	2003	Malaysia	\$0.67	no data	-	-	no data	-	-	3
Lamivudine+Zidovudine 150mg+300mg	2003	Zimbabwe	\$0.49	\$0.32 (0.18 – 0.45)	3 (3)	Int'l	\$0.51	1	CL	1
Lamivudine+Zidovudine 150mg+300mg	2004	Indonesia	\$0.81	\$0.35 (0.22 – 1.04)	13 (5)	Int'l	\$0.29 (0.22 – 3.67)	19 (9)	Int'l	5
Lopinavir+Ritonavir 133.3mg + 33.3mg	2003	Brazil	\$2.22	no data	-	-	no data	-	-	2
Lopinavir+Ritonavir 200mg+50mg	2006	Brazil	\$0.63	no data	-	-	\$0.56	1	Int'l	0
Lopinavir+Ritonavir 200mg+50mg	2007	Thailand	\$0.46	\$0.68 (0.68 – 0.68)	2 (2)	CL	\$0.34 (0.34 – 0.83)	17 (5)	Int'l	5
Lopinavir+Ritonavir	2010	Ecuador	\$0.57	\$0.34 (0.28 – 0.76)	14 (8)	Int'l	\$0.31 (0.28 –	52 (9)	Int'l	18

Product	Year	Nation	Post-CL	Patented in peer nation – median int'l price (min – max)	Patented in peer nation – # procurements (# nations)	Lower median (min) price	Not patented in peer nation – int'l median price (min – max)	Not patented in peer nation – # procurements (# nations)	Lower median (min) price	# buys where patent status not known
200mg+50mg							0.68)			
Lopinavir+Ritonavir 100mg+25mg	2010	Ecuador	\$0.32	\$0.38 (0.18 – 0.44)	6 (2)	CL (Int'l)	\$0.16	1	Int'l	0
Lopinavir+Ritonavir 80mg+20mg (90ml bottle)	2010	Ecuador	\$24.00	no data	-	-	\$16.77 (7.33 – 20.84)	13 (6)	Int'l	1
Lopinavir+Ritonavir 200mg+50mg	2010	Thailand	\$0.54	\$0.34 (0.28 – 0.76)	14 (8)	Int'l	\$0.31 (0.28 – 0.68)	52 (9)	Int'l	18
Nelfinavir 250mg	2003	Brazil	\$0.52	\$1.36	1	CL	no data	-	-	0
Nevirapine 200mg	2004	Indonesia	\$0.47	\$0.60 (0.09 – 0.68)	14 (6)	CL (Int'l)	\$0.11 (0.02 – 0.60)	11 (7)	Int'l	6
Ritonavir 100mg	2010	Ecuador	\$0.98	\$0.93 (0.92 -1.94)	3 (2)	Int'l	\$1.19 (0.11 – 2.21)	9 (6)	CL (Int'l)	4
Tenofovir 300mg	2006	Brazil	\$3.78	no data	-	-	\$2.26 (0.57 – 3.59)	6 (5)	Int'l	3
Tenofovir 300mg	2008	Brazil	\$3.80	no data	-	-	\$0.51 (0.42 – 1.28)	28 (11)	Int'l	4
Zidovudine 100mg	2003	Malaysia	\$0.16	no data	-	-	no data	-		1

Chapter 6 (Article 5):

Could patents interfere with the development of a cardiovascular polypill?

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6.1 Abstract

6.1.1 Background

The Wellcome Trust, the World Health Organization, and cardiologists have advocated for the idea of a “polypill” containing multiple cardiovascular drugs to be co-formulated into a single pill for over a decade. Some cardiologists have asserted that the drugs commonly considered for inclusion into such a polypill are older and therefore free of patent protection. We tested this assertion. This project was requested by the World Heart Federation (WHF).

6.1.2 Methods and materials

Two cardiologists from the WHF provided a list of 48 cardiovascular drugs for evaluation. We designated the United States and Canada as the base jurisdictions for this patent study. We linked patent data from these countries’ national medicine patent registers to patent information in over 96 other countries using Derwent and INPADOC via Thomson Innovation. We expanded our study beyond the aforementioned data linkage through a systematic search of WIPO PatentScope, which was based primarily upon the drugs’ active ingredient names.

6.1.3 Results

In the United States and Canada, 8 of the drugs were only available in the patent-protected, brand name formulation in one or both countries. Another 21 drugs had relevant patents, but generic equivalents were nevertheless available. Only 19 drugs (40%) appeared entirely post-patent. Broadening the co-formulation searches globally, the overwhelming majority of drugs (40/48) were mentioned in patent applications for cardiovascular drug combinations.

6.1.4 Conclusion

The assertion that most of these cardiovascular drugs are post-patent is accurate, but only in the sense that many of the original patents on these active ingredients have expired and that generic alternatives are usually available. The landscape of patents covering novel (co-) formulations is far more complex, however. Most research and development for cardiovascular

combination medicines are likely to be undertaken by companies whose original patents on the active ingredient will soon expire or have recently expired. Cardiologists looking to accelerate polypill development may consider approaching such companies to partner.

6.2 Introduction

There is a major gap between the prevalence of hypertension, and recourse to effective treatment, particularly in developing countries, where 80 percent of the disease burden lies (1, 2). To address this, many have called for simplifying both the prescribing of and adherence to treatment by co-formulating (i.e., combining) several drugs into a single “polypill,” rather than 3-7 pills taken individually (3-6). Triple and even quadruple co-formulations have been developed for conditions such as HIV/AIDS and tuberculosis, and are credited with improved treatment outcomes (7, 8). A number of clinical trials (2, 9, 10) and meta-analyses (11, 12) of different polypill co-formulations suggest that the same strategy can be helpful for the treatment of hypertension and for the primary and secondary prevention of cardiovascular disease (CVD) (13, 14). A polypill can also improve adherence, and it can reduce the risk of adverse drug interactions in patients taking multiple medications (15). Given the potential to reduce cardiovascular events and the associated cost of care, public investment into the development of a polypill has been shown to be cost-effective (16). Indeed, the World Health Organization has been calling for the development of a polypill for over a decade (17).

But while there is large appetite from the public health community for a polypill, no such thing is commonplace in today’s global pharmaceutical market. Why is this? Are there patent barriers to market entry? Experts on the treatment of cardiovascular disease have stated that the drugs under consideration for inclusion in cardiovascular polypill prototypes are no longer covered by patents (3, 6, 18), but this presumption has not been rigorously tested. A very recent study was published that investigated the patent situation on five cardiovascular medicines in the United States and Europe, but did not extend beyond these drugs and geographic regions (19). Several publications, both academic (4, 20) and otherwise (21, 22), have rightly called for a broad and global understanding of the polypill patent situation. This article is intended to address this need. It

is written for a broad audience while bearing in mind that this project was undertaken at the request of the World Heart Federation (WHF).

6.3 Methods and materials

We began by independently consulting two expert cardiologists (JDRS, MDH)—who both participated in a workshop on the polypill endorsed by the WHF—on what drugs are of particular interest for co-formulating. We used the union of their drug lists (n=48 drugs) as the focal point for this patent study.

As patent grants vary by country, it is necessary to designate a base legal jurisdiction for patent studies as a starting point for analysis. Consistent with other published methodologies (23-29), we set the United States and Canada as our base jurisdictions because medicine patents are uniquely prevalent there. These countries have large pharmaceutical markets, grant a high number of patents annually, and have strong infrastructure for enforcing those patents, making them particularly attractive for pharmaceutical suppliers.

Both countries have publicly available medicine patent registers—the United States Food and Drug Administration’s Orange Book (30) and Health Canada’s Patent Register (31)—that allow users to search by active ingredient name. We therefore searched by each active ingredient name in each database and then recorded the patent information retrieved, if any. We also recorded whether an equivalent generic product was available on the market for each drug using the Orange Book (30) and Health Canada’s Drug Product Database (32)—that is to say, whether the product had already been “genericized” in the United States and Canada respectively. We considered an equivalent to be a generic product with the identical active ingredient(s), (co-)formulation, and strength as the brand name one in question (i.e., the originator’s patented version).

Next, we consulted two commercial-grade international patent search databases covering over 96 countries—INPADOC (33) and Derwent (34)—via Thomson Innovation (35). These databases group patent filings into “patent families” (i.e., sets of related patents), which is either

done automatically by their relationship to an original priority application (as is the case in INPADOC (36)) or is done manually by patent analysts (as is the case in Derwent). Using the union of the patent family groupings of INPADOC and Derwent adds to the robustness of studies such as these, both in terms of the type of patents covered and the countries covered by them (23). We entered the American and Canadian patent data from those North American medicine patent registers into Thomson Innovation and retrieved the international patent families for each drug. Reasoning that patent protection for each application is unlikely to extend longer than the standard 20-year period, we removed all patents with application filing dates earlier than 1 January 1995.

Thereafter, we reviewed the title and abstract of each “Basic” patent identified by Derwent (i.e., a patent representing the typical one contained within each family). We scored the type of protections typically covered by the patents contained in each family according to their proposal of a new co-formulation (i.e., drug combinations), a new compound (i.e., the active ingredient), a new formulation (e.g., extended release tablet or capsule), a new method of treatment (i.e., using the drug to treat specific conditions), and/or a new manufacturing process.

Both a strength and limitation of the above method is that all patents included are related to currently marketed products. To provide an impression of potentially relevant patent literature that may have been excluded, we conducted supplemental searches in the World Intellectual Property Organization’s (WIPO) PatentScope database (37). This database contains applications filed by those seeking protection in many or all of the 148 national signatories to the Patent Cooperation Treaty. We built search algorithms to capture patent applications on combinations of the drugs on our list of 48 medicines.

All of the above patent searches were performed in May and June 2015. Note that there is no objective, definitive point at which such searches have identified all relevant patents. An expert judgment has to be made when to stop. Our results therefore should be taken as a preliminary appraisal, reflecting our search strategy, and should not be regarded by anyone seeking to

commercialize these drugs as a substitute for obtaining independent legal advice. Our raw datasets are available in this article's supplementary materials.

6.4 Results

6.4.1 The drugs' patent/genericized status as single formulations in the United States and Canada

We found that 8 of the 48 drugs (17 percent) were available only as a brand name, patent-protected formulation in one of the base jurisdictions (the United States or Canada) (see Figure 6.9.1). Olmesartan was the only drug available exclusively in the brand name in both countries.

Also shown in Figure 6.9.1 are the 16 drugs (33 percent) for which relevant patents were located in the United States or Canada, but had nevertheless been genericized. As for the remaining cardiovascular drugs (24 of 48 or 50 percent), we located no valid patents and observed that the markets had indeed been genericized.

6.4.2 The drugs' patent/genericized status as co-formulations in the United States and Canada

As for fixed-dose combination (FDC) products containing one or more of the 48 drugs of interest, we found 10 drugs (21 percent) for which the only co-formulation(s) available in the United States or Canada was the patent-protected, brand name product. See Figure 6.9.2. An additional 10 drugs (21 percent) were contained in one or more patented-protected FDCs, but had been genericized. For the majority of the cardiovascular drugs (28 of 48, or 58 percent) investigated, however, we either located no patents using our methodology or observed that no co-formulations containing the drug in question were on the market.

6.4.3 Patent filings by type of protection and by country

Table 6.8.1 shows the type of protections covered by the patent filings contained in the INPADOC and/or Derwent international patent families relating to the relevant US or Canadian

marketed products in question. Patent protection on these drugs' active ingredients was rare, but in some cases, not all patents had expired globally, even in North America.

By far, the most common type of protection afforded by these drugs' respective patent families pertained to novel formulations or co-formulations. Patents applying to these categories were nearly five times more prevalent as compared to those on the active ingredient. Patents on using the drug as a method of treatment for cardiovascular disease or on a manufacturing process were also much more common than those on the active ingredient.

Nevertheless, as is shown in Table 6.8.1, we found no patents of any type whatsoever on 19 of these drugs in the United States and Canada, which cover all drug classes identified by the WHF cardiologists (i.e., statins, antiplatelets, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta blockers, and diuretics).

6.4.5 Searching for polypill co-formulation patents globally: WIPO PatentScope

Finally, to extend our analysis beyond the patents related to those listed in the American and Canadian medicine patent registers, we searched WIPO PatentScope for all patent applications that mention combinations of drugs within our list of 48 cardiovascular medicines. (See Appendix 6.10.1 for four common approaches that we observed applicants had taken to construct their patent applications for cardiovascular FDCs.)

The overwhelming majority of the drugs (40 of 48, or 83 percent) were identified in the co-formulation patent applications returned from WIPO PatentScope, either by active ingredient name or by drug class. Only 8 drugs were unmentioned, all of which were older diuretics (amiloride, bumetanide, chlorthalidone, eplerenone, furosemide, metolazone, spironolactone, torasemide, triamterene). The remaining 3 (chlorothiazide, hydrochlorothiazide, indapamide) were identified as the diuretic of choice in many proposed co-formulations, especially hydrochlorothiazide.

6.5 Discussion

Cardiologists' perception (3, 6, 18) that the drugs being considered for CVD polypill co-formulations are post-patent has some empirical merit, but only in the sense that many of the original patents on the active ingredient(s) have expired and that the majority of these drugs have been genericized. This overlooks, however, the other forms of patent protection (i.e., formulation, co-formulation, method of treatment, manufacturing process) that are more prevalent and that can carry on for years after the expiration of the original patents on the active ingredient(s). We found that only 19 of the 48 drugs (40 percent) were totally patent free in the base jurisdictions according to our methodology (see Table 6.8.1) and that most of the drugs (40 of 49, or 83 percent) could be found on co-formulation patent applications filed through WIPO. When these secondary tiers of patenting are taken into account, it is more common to find patent filings than none whatsoever.

What is the significance of this finding for polypill advocates like the WHF who see promise in that treatment in developing countries? Below we discuss two perspectives on the patent system—for shorthand, the competitive versus cooperative perspectives—which differently inform two corresponding courses of action based on the findings and data presented in this report.

The "competitive" perspective is that patents represent strong, if temporary, barriers for others seeking to develop a technology and disseminate it widely. Patent owners possess exclusive rights to seek financial compensation in the law courts from those who infringe their technology. In this perspective, advocates of a CVD polypill should be prepared to deal with risk adverse pharmaceutical companies, who would likely not want to develop products that infringe upon these rights. Any patent is therefore a disincentive.

Based on this view of the patent system, our results, such as those in Table 6.8.1, may be read as a road map of existing obstacles to polypill co-formulating, while the non-shaded areas of Figures 6.9.1-6.9.2 represent the patent-free freedom to operate. One could, then, work within the latter subset to propose a new cardiovascular FDC, which dodges the patent barriers. In doing so,

advocates would be well advised to work with pharmaceutical firms with proven track records in the chemistry, manufacturing and controls aspects of making pharmaceuticals and with experience obtaining product registration. While all the major pharmaceutical companies have these capacities, some generics firms do as well. As of writing, one generics company (Ferrer) is already making FDCs that meet the requirements of stringent regulatory authorities in Europe, as are several India-based firms albeit without satisfying stringent regulatory authority standards (17, 38).

The "cooperative" perspective is that the patent system serves to incentivize new innovation, products and commercial activities. Patent owners acquire rights so as to make a business case for investment and commercialization. In this perspective, advocates of a CVD polypill should try to piggyback onto efforts that maximize the revenue pharmaceutical companies can obtain from their patent holdings, but in such a way that allowances are made for access to medicines in poorer countries.

Based on this view of the patent system, the shaded areas of Figures 6.9.1-6.9.2 represent not barriers, but opportunities, because the patent holder's exclusivity brings with it a company that already has solved the technical and regulatory issues of their patented drug, and likely has the wherewithal and business interest to drive forward a new FDC including that drug. Indeed, evidence shows that companies become most receptive to develop new co-formulations as primary patents come close to expiring, so as to extend (or "evergreen") market exclusivity (39). See Table 6.8.2 for the age original patents on the active ingredients of the 48 drugs' in descending order according to the Merck Index (40). There is empirical evidence that co-formulating is already happening for the most recently expired patents on the active ingredients: Daiichi Sankyo has recently introduced Tribenzor (amlodipine + hydrochlorothiazide + olmesartan), and Novartis has introduced Exforge HCT (the same, but substituting valsartan for olmesartan). Advocates would be well advised to create mutually beneficial arrangements with the pharmaceutical companies whose

original patents on the active ingredient are drawing to an end, both to innovate polypills, and to bring these to market in developing countries at an affordable price. A clear lesson learned from the global campaigns for access to HIV/AIDS, malaria and other medicines is that companies can reconcile revenue maximization in rich countries with reduced revenue expectations or even philanthropic concessions in poor countries. They can do this by out-licensing their patents in the latter, refraining from enforcing their patents in certain regions, and/or offering substantial price reductions based on ability to pay (tiered pricing) (41-45). Whatever access strategy is chosen, patents are actively managed to serve as springboards for access campaigns, rather than managed as just barriers.

We do not consider the "cooperative" and "competitive" scenarios mutually exclusive; rather they are complementary and should both be pursued. But both of them require that advocates make it extremely clear *exactly* which medicine combinations are best for an FDC. That choice has to be based on strong scientific consensus of the most clinically rational combinations, but not necessarily unanimity, and must strike a balance between the best therapeutic outcomes (for treatment success) and widespread suitability of the formulation (for population health coverage). Clear consensus is a true *sine qua non*, because whether seen through the eyes of a branded or generic company, advocates are calling on them to invest millions of dollars in FDC development and registration—and very simply put, companies will only sink that money when there is consensus guidance that says "the combination of A plus B plus C is satisfactory", rather than equivocal guidance that says "the combination of A or B, plus C or D, plus E or F, but not if F is combined with C".

The endorsement of advocates, or a coalition of advocates, to recommend a particular CVD co-formulation would likely appeal to drug makers and have a very significant impact on their willingness to invest. Since one would be endorsing a choice of co-formulation, and not a product, there is no conflict of interest in doing so. That would be a valuable step, whether pursuing a FDC

built upon the "competitive" viewpoint of selecting only unpatented drugs over which nobody has exclusivity, or upon the "cooperative" viewpoint of selecting a drug precisely because it is patented and somebody has exclusivity. Our previous research in bringing low-cost new medicines to developing countries has shown that, depending upon circumstances, patent-centered strategies for improving access to medicines can be just as effective as patent-negating ones (41, 46, 47).

5.6 Conclusion

Our study has tested the assertion that the drugs under consideration for polypill co-formulating are older, are post-patent, and have been genericized. For the original, active ingredient patents, this is largely true, but our findings show that secondary patenting on these medicines is prevalent, and this includes large numbers co-formulation patents by generic and brand name companies alike.

We have suggested two strategies based on the empirical data provided by this study for global public health entities like the WHF who are in pursuit of developing a polypill, and these strategies can be undertaken simultaneously. Our impression, however, is that others attempting to advance polypill development have relied most heavily upon variants of the first strategy. We suggest a more balanced approach, set upon two parallel tracks, in which patents are viewed as both barriers, and opportunities, depending who the commercial partner is.

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6.8 Tables

Table 6.8.1 – The 48 cardiovascular drugs categorized by type of patent protection and country

Drug	United States					Canada					Other countries				
	Patents ¹					Patents ¹					Patents ²				
	Co-formulation	Compound	Formulation	Method	Process	Co-formulation	Compound	Formulation	Method	Process	Co-formulation	Compound	Formulation	Method	Process
acebutolol															
acetylsalicylic acid (aspirin)			X	X				x	x				16	16	
amiloride															
amlodipine	X		x	x	x	X					63	1	4	7	4
atenolol															
atorvastatin	X		X	x	X	X		X	X	X	50	4	53	39	39
benazepril	X														
bisoprolol															
bumetanide															
candesartan	X	x		x				x	x	x	1		4	10	9
carvedilol			X	X	X			x	x	x			22	29	13
chlorothiazide															
chlorthalidone	X										x				31
clopidogrel			X		X					X			11	44	44
enalapril													3		
eplerenone	X		X	X		x		x	x		25	3	25	25	
eprosartan	X		X	X	X	X		X	X	X	7	6	37	42	37
felodipine															
fluvastatin			X						X				36		
fosinopril													2		
furosemide															
hydrochlorothiazide	X					X					60				
indapamide	x					X					37				
irbesartan	X		X			X		X			23	8	23		
lisinopril													3		
losartan			x		x								2		
lovastatin	X		X					x			13	1	12	12	
metolazone															
metoprolol															
nadolol															
nebivolol			X					x					1	31	4
nifedipine															

Drug	United States					Canada					Other countries					
	Patents ¹					Patents ¹					Patents ²					
	Co-formulation	Compound	Formulation	Method	Process	Co-formulation	Compound	Formulation	Method	Process	Co-formulation	Compound	Formulation	Method	Process	
nimodipine																
olmesartan	X	X	<i>x</i>	<i>x</i>	<i>x</i>	<i>x</i>	<i>x</i>				<i>29</i>	<i>8</i>	<i>24</i>	<i>8</i>	<i>8</i>	
perindopril			<i>x</i>	<i>x</i>	<i>x</i>	X	X	X	X		<i>18</i>		<i>37</i>	<i>18</i>		
pitavastatin	X		X	X	X		<i>x</i>	<i>x</i>	<i>x</i>		<i>13</i>	<i>2</i>	<i>17</i>	<i>17</i>	<i>10</i>	
pravastatin				X				<i>x</i>				<i>1</i>		<i>8</i>		
propranolol			X	X			<i>x</i>	<i>x</i>					<i>10</i>	<i>10</i>		
quinapril			X	X		X						<i>1</i>	<i>3</i>	<i>3</i>		
ramipril	X			X		X			X		<i>34</i>		<i>34</i>	<i>35</i>		
rosuvastatin		X	X	X				X	X		<i>6</i>	<i>50</i>	<i>33</i>			
simvastatin	X					X					<i>19</i>					
spironolactone																
telmisartan	X	<i>x</i>	X	X	X	X	X	X	X		<i>49</i>	<i>6</i>	<i>35</i>	<i>17</i>	<i>36</i>	
torasemide																
trandolapril	X			X			X		X		<i>3</i>			<i>2</i>		
triamterene																
valsartan	X	<i>x</i>	X	X		X	X	X			<i>42</i>	<i>7</i>	<i>36</i>	<i>36</i>		
Total	18	5	20	18	10	1	1	1			52	12	53	33	20	
						4	2	8	4	9	3	0	6	8	0	
	All countries															
Grand totals	55	12	57	37	21											
	5	7	4	0	9											

¹ A bold "X" means that at least one patent was found fitting into this category on the national patent register. A italic "X" denotes at least one patent was found in the INPADOC and/or Derwent Patent Family, but current legal status is unknown.

² The numbers below indicate the number of jurisdictions (countries or regional agreements) covered by the patents in the INPADOC and Derwent Patent Families. Current legal status of these patents is unknown.

Table 6.8.2 – Merck Index active ingredient patent listing for the 48 cardiovascular drugs

INN	Latest patent grant year provided	International INPADOC family application date range	Patent numbers provided
olmesartan	1997	1992 - 2011	EP503785, US5616599
valsartan	1995	1991 - 2010	EP443983, US5399578
candesartan	1993	1991 - 2006	EP459136, US5196444
eprosartan	1993	1990 - 2001	EP403159, US5185351
irbesartan	1993	1990 - 1999	WO9114679, US5270317
atorvastatin	1993	1990 - 2007	EP409281, US5273995
rosuvastatin	1993	1992 - 2003	EP521471, US5260440
losartan	1992	1987 - 1999	EP253310, US5138069
telmisartan	1992	1991 - 2011	EP502314
fosinopril	1991	1988 - 1995	EP 304063, US5011930
pitavastatin	1991	1988 - 1995	EP304063, US5011930
trandolapril	1990	1981 - 1994	EP84164, US4933361
clopidogrel	1989	1982 - 1998	EP99802, US4529596, EP281459, US4847265
fluvastatin	1988	1983 - 1995	WO8402131, US4739073
nebivolol	1987	1984 - 2004	EP145067, US4654362
ramipril	1986	1982 - 1994	EP79022, US4587258
amlodipine	1986	1983 - 1998	EP89167, US4572909
perindopril	1985	1979 - 1993	EP49658, US4508729
carvedilol	1985	1978 - 1994	DE2815926, US4503067
eplerenone	1985	1984 - 2004	EP122232, US4559332
simvastatin	1984	1980 - 1994	EP33538, US4444784
benazepril	1983	1982 - 1993	EP72352, US4410520
enalapril	1983	1979 - 1998	EP12401, US4374829
lisinopril	1983	1979 - 1998	EP12401, US4374829
quinapril	1982	1981 - 1996	EP49605, US4344949
pravastatin	1982	1980 - 1996	DE3122499, US4346227
felodipine	1981	1978 - 1994	EP7293, US4264611
bisoprolol	1981	1976 - 1993	BE859425, US4258062
lovastatin	1980	1978 - 1998	US4231938
torasemide	1977	1974 - 1994	DE2516025, US4018929
metoprolol	1976	1932 - 1977	DE2106209, US3998790
nadolol	1976	1971 - 1979	DE2258995, US3935267, DE2421549
nimodipine	1974	1971 - 1977	DE2117571, US3799934
acebutolol	1974	1967 - 1974	ZA6808345, US3857952
atenolol	1974	1969 - 1975	DE2007751, US3663607, US3836671

INN	Latest patent grant year provided	International INPADOC family application date range	Patent numbers provided
bumetanide	1974	1968 - 1974	DE1964503, DE1964504, US3806534
indapamide	1971	1968 - 1969	FR2003311, US3565911
propranolol	1970	1962 - 1967	BE640312, BE640313, US3337628, US3520919
nifedipine	1969	1967 - 1969	ZA6801482, US3485847
amiloride	1967	1962 - 1981	BE639386, US3313813
metolazone	1967	1966 - 1967	US3360518
acetylsalicylic acid (aspirin)	1966	1959 - 1964	DE236196, US2890240, US3235583
hydrochlorothiazide	1964	1962 - 1965	US3025292, US3163645, DE1163332, US3164588, US3043840
triamterene	1963	1960 - 1964	US3081230
chlorthalidone	1962	1957 - 1962	US3055904
furosemide	1962	1959 - 1964	DE1122541, US305888
spironolactone	1961	1960 - 1961	US3013012
chlorothiazide	1957	1957	US2809194

6.9 Figures

Figure 6.9.1 – The 48 cardiovascular drugs *as single formulations* categorized by presence of generic competition and active patent listings in the United States or Canada

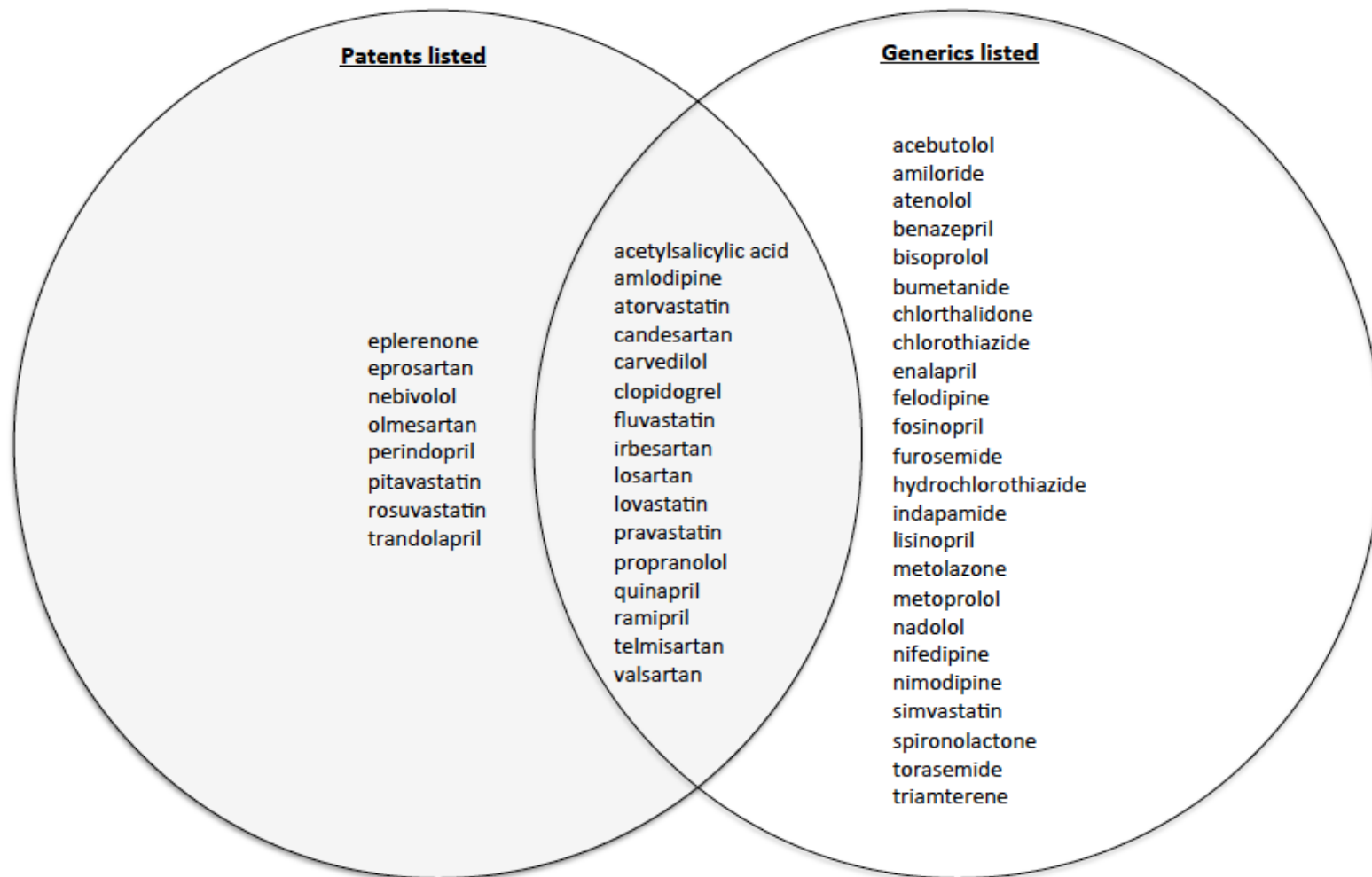
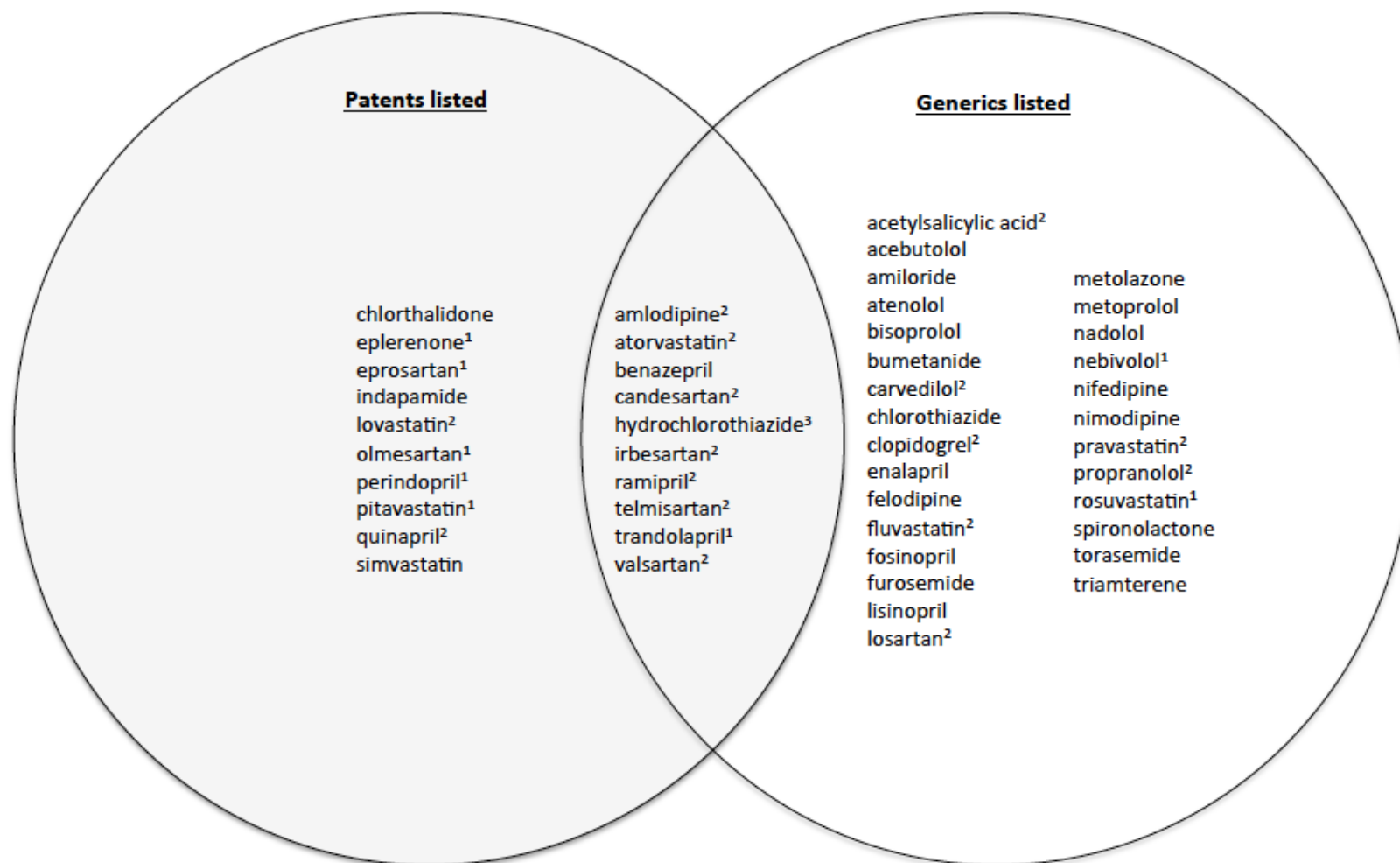


Figure 6.9.2 – The 48 cardiovascular drugs in FDCs categorized by presence of generic competition and active patent listings in the United States or Canada



¹ This drug has one or more patents listed for it as a single formulation matched with an absence of generic alternatives in the concerned market (see Figure 6.9.1).

² While this drug has one or more patents listed for it as a single formulation, there are nevertheless generic alternatives available in that market (see Figure 6.9.1).

6.10 Appendices

Appendix 6.10.1 – Typology of search results from co-formulation searches in WIPO PatentScope

Our iterative process used three searches, incorporating increasingly specific criteria to locate patent applications that describe cardiovascular co-formulations made from combinations of the 48 drugs of interest; these searches returned 211, 178, 14 publications respectively. We observed that the patent applications were constructed according to one of the following four approaches below. Patents have been granted for applications falling into all four of these categories (especially those naming very specific fixed dose combinations), but not consistently so. The final category, which is the most vague and far-reaching, appeared to be the most difficult to patent; while we observed grants on such applications in some jurisdictions, we saw several denials in other places.

Application approach	Example	Analysis
One specific active ingredient with <i>any</i> other active ingredient	WO/2010/036600 by Merck states that its formulation patent application applies to “atorvastatin as the only active agent or combined with one or more additional active agents.”	Should these patents be granted in the relevant country, these patents may block development. It is often the case, however, that the original compound and/or formulation patent has already (or should have already) laid out this claim and has since expired.
Two or more specific active ingredient combinations	WO/2013/100630 by Hanmi Pharmaceuticals proposes a FDC of amlodipine + hydrochlorothiazide + valsartan. An extreme example is Cipla’s WO/2009/087410, which lists all 33 ingredients under consideration for co-formulations (8 of these ingredients were on our list) (note that this patent application has since been abandoned).	These can be handled as traditional FDC patents. Should such a patent be granted in the relevant jurisdiction and should it include the same ingredients in one’s polypill recipe or be reasonably similar, it is worth following up and consulting legal advice before proceeding. Many FDC patents are proposed and later abandoned due to factors like manufacturing feasibility.
One specific active ingredient with an	Wockhardt Limited’s WO/2013/084089	Other classifications may be rather specific

Application approach	Example	Analysis
ingredient from one or more other ingredient classification(s)	states: "...fixed dose combination of metoprolol in extended release form and one or more calcium channel blocker, angiotensin II receptor blocker or angiotensin converting enzyme inhibitor along with one or more rate controlling excipient."	(e.g., a HMG-CoA reductase inhibitor (statins)) or more general (e.g., at least one other active agent, wherein the at least one other active agent is a cardiovascular agent). The more specific are more concerning. Should such a patent be granted in the relevant jurisdiction with a fairly specific and similar prototype description, further legal investigation is necessary.
One or more active ingredient classifications with other classifications for treating specific conditions	Novartis' WO/2006/116435 is illustrative, describing the invention as including "...at least one therapeutic agent selected from the group consisting of: (1) an ACE inhibitor, or a pharmaceutically acceptable salt thereof; (2) an angiotensin II receptor blocker, or a pharmaceutically acceptable salt thereof; (3) a diuretic, or a pharmaceutically acceptable salt thereof; (4) a calcium channel blocker (CCB), or a pharmaceutically acceptable salt thereof; (5) a beta-blocker, or a pharmaceutically acceptable salt thereof; (6) a platelet aggregation inhibitor, or a pharmaceutically acceptable salt thereof; (7) a cholesterol absorption modulator, or a pharmaceutically acceptable salt thereof; (8) a HMG-Co-A reductase inhibitor, or a pharmaceutically acceptable salt thereof; and (9) a high density lipoprotein (HDL) increasing compound, or a pharmaceutically acceptable salt thereof."	Specific categories are named with several active ingredients as examples (e.g., a statin such as atorvastatin, lovastatin, or simvastatin). They also tend to describe the combination as treatment for one or more target illnesses. These applications are clearly filed by those in pursuit of developing a polypill. Should these applications closely describe the one's polypill prototype for the same medical condition and be granted in the relevant jurisdiction, it would be important to follow up and seek legal advice. Simple adjustments to already patented combinations may be considered too obvious for a patent to be granted.

Chapter 7 (Article 6):

Is patent “evergreening” restricting access to medicine/device combination products?

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7.1 Abstract

7.1.1 Background

Not all new drug products are truly new. Some are the result of marginal innovation and incremental patenting of existing products, but in such a way that confers no major therapeutic improvement. This phenomenon, pejoratively known as “evergreening”, can allow manufacturers to preserve market exclusivity, but without significantly bettering the standard of care. Other studies speculate that evergreening is especially problematic for medicine/device combination products, because patents on the device component may outlast expired patents on the medicine component, and thereby keep competing, possibly less-expensive generic products off the market.

7.1.2 Methods and materials

We focused on four common conditions that are often treated by medicine/device product combinations: asthma and chronic obstructive pulmonary disease (COPD), diabetes, and severe allergic reactions. The patent data for a sample of such products (n=49) for treating these conditions was extracted from the United States Food and Drug Administration’s Orange Book. Additional patent-related data (abstracts, claims, etc) were retrieved using LexisNexis TotalPatent. Comparisons were then made between each product’s device patents and medicine patents.

7.1.3 Results

Unexpired device patents exist for 90 percent of the 49 medicine/device product combinations studied, and were the only sort of unexpired patent for 14 products. Overall, 55 percent of the 235 patents found by our study were device patents. Comparing the last-to-expire device patent to that of the last-to-expire active ingredient patent, the median additional years of patent protection afforded by device patents was 4.7 years (range: 1.3 – 15.2 years).

7.1.4 Conclusion

Incremental, patentable innovation in devices to extend the overall patent protection of medicine/device product combinations is very common. Whether this constitutes “evergreening” depends on whether these incremental innovations and the years of extra patent protection they confer are proportionately matched by therapeutic improvements in the standard of care, which is highly debatable.

7.2 Introduction

Many medicines are inextricably paired with specific devices for administering them. Asthma, chronic obstructive pulmonary disease (COPD), diabetes, and severe allergic reactions are examples of common conditions that, depending on the medicine prescribed, may come with a proprietary inhaler or injector that is integrated into the product design.

What may not be obvious is that in these combinations, the medicine and the device are separately patentable. Thus, even after all the patents on the medicine expire, remaining patents on the associated device, or parts thereof, can prevent generic competitors from emerging. In other words, medicine patents and device patents are not coextensive, but synergistic—a relationship companies can use strategically to prolong market exclusivity (1).

For example, in 2008 when the United States' Food and Drug Administration (USFDA) mandated that all metered-dose inhalers stop using ozone-depleting chlorofluorocarbon (CFC) propellants, pharmaceutical companies switched to hydrofluoroalkane (HFA) propellants (2). Albuterol, for example, is a common medication prescribed for both asthma and COPD, and is old and off-patent, but new HFA-compatible valves, elastomers, and surfactants were needed to comply with new USFDA requirements, resulting in new patentable devices (3). The new, proprietary HFA-based albuterol-containing products entered the market at double or triple the price of the old, generic CFC-based products (4). Similar price movements have been observed for human insulin, which despite being an old and off-patent has no generic competition in the United States (5).

The patent system's *raison d'être* is based, however imperfectly, on the social bargain that the market exclusivity of a 20-year patent incents and rewards worthwhile inventions. It is therefore debatable whether incremental device innovation and patenting creates proportionate therapeutic improvements (or environmental improvements, in the

case of HFA-based inhalers) (6-9). The term “evergreening” has been coined to disparage the practice of making incremental, patentable inventions for medicines without corresponding benefit, particularly if patients are aggressively or forcibly transitioned to the new product: examples include omeprazole versus esomeprazole, or memantine versus memantine extended release (10). This paper explores the possible salience of evergreening to devices, which has received less attention (1, 5, 9-11).

This is the first study known to the authors to analyze the effect of medicine/device patent synergies in several therapeutic areas where they prevail: inhaled medicines for treating asthma and COPD, auto-injectors for treating anaphylaxis, and insulin pens for the treatment of type 1 (insulin dependent) diabetes. We test the hypothesis that having two modes of patenting, rather than one, prolongs product exclusivities. Where this is the case, it can negatively affect health by precluding competition that reduces prices, as is anecdotally observed. Our study explores the mechanism whereby this can happen.

7.3 Methods and materials

Products such as auto-inject pens or inhalers sold pre-loaded with the active ingredient qualify for inclusion on the USFDA’s “Orange Book” because that regulator considers them inseparable from the medicines that contain them. The Orange Book is an online database that lists the United States patent holdings of most medicines with FDA marketing approval. The Orange Book however has limitations: it only includes devices primarily associated with the medicine, and not necessarily those secondarily associated (e.g., insulin pumps or continuous glucose monitors) (1).

We identified and included all insulin or epinephrine device products in the Orange Book (12) by searching for the name of the active ingredient, regardless of patent status. For our sample of asthma and COPD medicines, we located all patent data in the Orange Book for all products on the USFDA’s list of asthma and COPD medicines (13). After

compiling the Orange Book patent data (including patent numbers and expiration dates), additional information on each of these patents (titles, abstracts, claims, etc) was extracted from the LexisNexis' Total Patent® database (14). This produced lists of patents pertaining to the medicine and device components of each combination product.

We categorized each patent by its applicability to the device or to the compound. The expiration date of the last-to-expire (co-) formulation or compound patent on the active ingredient was then identified and compared to the expiration date of its last-to-expire device patent. Using the Orange Book, we further documented the number of suppliers offering an equivalent medicine/device combination (i.e., one with an identical active ingredient, formulation, strength, and route of administration) in order to provide an impression of the level of exclusivity within these markets.

7.4 Results

Our main results are detailed in Table 7.7.1. All of the results outlined in this section are based on these data. Our search returned a total of 49 medicine/device combination products—32 inhalers containing an asthma or COPD medicine, 3 pens containing epinephrine, and 14 products involving an insulin-containing device, either a pen or inhaler.

7.4.1 Combination Product's device patent portfolios versus other patents

Table 7.7.1 lists the number of patents directed to a device versus those directed to the active ingredient alone. Nearly all combination products (44 of 49 products or 90 percent) listed at least one patent on aspects of the delivery device itself. The median, rather than the average (an indicator more sensitive to outliers), combination product had 3 device patents listed and only 2 on the medicament.

Overall, our data extraction from the Orange Book yielded 235 patents. Of these, 55 percent (n=129) are patents on the device. These outcomes demonstrate that, at least with

respect to a simple count of what is listed in the Orange Book, a given combination product in our sample has more patents on the device relative to all other categories.

We further importantly observe that 14 combination products (14/49 or 28.5 percent) only listed device patents (i.e., all patents on the active ingredient have expired or never existed) illustrating that patent activity on the device can continue well beyond the expiration of the patent on the medicine it delivers.

7.4.2 Length of remaining patent protection afforded by device patents

Figure 7.8.1 depicts the relative frequency of patent protection extensions evident in the 49 products as defined by the outcome typology indicated in the final column of Table 7.7.1. Patent protection extensions via the device was the case in 40 of 49 (82 percent) of the combination products investigated.

As for how many years of patent protection was gained through device patenting, two comparisons are possible. The first included those combination products for which both device and medicine patents were listed. This comparison was possible for 35 products in the sample (35/49 or 71 percent). Of these 35 products, 26 had a device patent expiration date that was later than the active ingredient patent expiration date. The median difference between these dates was 4.7 years. The most extreme case was Atrovent HFA®, with 15.2 years between the date of the last-to-expire active ingredient and last-to-expire device patent. The smallest gap was 1.3 years, for the lower dose of Afrezza®, the very new inhaled human insulin product by Sanofi.

The second comparison was for the 14 products for which only device patents were listed. Using the time of writing as the baseline (15 August 2015), the average combination product had 7.1 years of patent protection remaining by way of the device (an expiration year of 2022). The median number of added years was 9.0 as there were several combination products with large incremental patent life due to the device alone. AUVI-Q®,

for example, had a device patent expiring in 2029 (14.2 years) and ProAir Respiclick® had one expiring in 2027 (12.6 years).

7.4.3 Prevalence of market exclusivity

Because of device patents, none of these combination products included in this study are entirely off-patent. According to the Merck Index (a scientific reference publication that lists patents of therapeutic compounds) (15), 37 percent of the products in our sample have an original compound patent that expired prior to the year 2000 and yet all device/compound combination products in our sample listed at least one unexpired patent.

There was little competition present in the market for these combination products, as each one was typically the only one on the market with its active ingredient(s), (co-) formulation, strength, and route of administration. Table 7.7.1 quantifies the number of suppliers carrying an equivalent combination product. Of the 49 combination products analyzed, there was only more than one supplier for formulations of albuterol, albuterol + ipratropium, and epinephrine. Interestingly, in the cases of albuterol and epinephrine, all suppliers were offering their own branded, patented combination product for the same drug formulation.

7.8.5 Discussion

In our sample, there were more active patents listed, and with later expiration dates, on the devices as opposed to the medicine itself. This result is in part due to the fact that device components are typically developed (and therefore patented) after that of the active ingredient, allowing the patent portfolio of these combination products to extend for several additional years, due to the younger device patent.

Our study demonstrates that medicines for which patents have long expired in the United States can be placed behind a second tier of patent protection for their delivery

devices. Whether this is “evergreening”, however, requires consideration of that pejorative term. Underlying any such assessment is the reasoning that the state should only offer patents, which are private rights, in exchange for a proportionate public benefit. However, there is no single, agreed-upon, rigorous definition of evergreening in the literature, so any conclusion in this regard is open to debate. Our results allow for a more nuanced consideration of how the term should be defined in the future, and we propose both general and health-specific definitions here.

In the general definition, evergreening occurs when a secondary patent extends the product’s exclusivity period without a proportionate benefit of any sort. Under this definition, many of the allergy and diabetes products in this study arguably were evergreened by device patents, because there appears to be no therapeutic benefit, but the asthma and COPD inhalers that were originally available with a CFC propellant were not evergreened, because of the environmental benefit in switching from ozone-depleting CFC to safer HFA propellants. (Although with this example, even though there is no therapeutic benefit, there is arguably an ultimate public health benefit of an intact ozone layer).

In the health-specific definition, evergreening occurs when a secondary patent extends the product’s exclusivity period without a proportionate therapeutic benefit. Under this definition, many of the products in this study were arguably evergreened, because the medicines would have the same (or very nearly so) therapeutic benefit if administered by an alternative device. We note, however, that some new devices do offer a therapeutic benefit, for example new MDIs that improve particle deposition, which may allow for a smaller amount of a medicine to be administered (16). These situations do not neatly fit into our definition of evergreening, but may still allow for prolonged market exclusivity, as subsequent entrants would need to invest in research and development of a new device of

comparable efficacy to the existing device with a valid patent, which undoubtedly reduces the profitability of generic versions of the medicine.

Whether the health-specific or the general definition of evergreening is to be preferred is not an appropriate subject for this paper. We do note, however, that one's view on this distinction is fundamental to agreements or disagreements about the value of device patents such as those studied here. In particular, any government considering legislative action against evergreening (and some already have, such as India) needs to form a clear definition first (17).

When companies can evergreen device-intensive combination products this may foster perverse incentives for originators to, for instance, turn injectable active ingredients into device-intensive combination products or to develop "device-intensive routes" over other options. Given the number of parts on any device, there are multiple independent components to improve and update continuously, opening the door to incremental patenting that presents opportunities for evergreening by layering device patents upon device patents. If left unchecked, the patent system's weakness for incentivizing patentable ideas rather than the most therapeutically beneficial ones (18) could misdirect research and development dollars into developing new devices when the old ones would do, and/or avoiding more therapeutically beneficial designs that may not be patentable.

Combivent Respimat® is a good example of this. The original patents on the compounds (albuterol and ipratropium) were granted in 1972 and 1970 (15) respectively and have therefore been post-patent for over 25 years. Today these active ingredients are attached to an inhaler that, while appearing a simple device, bears 17 patents with expiration dates ranging from 2014 to 2028. Boehringer, which held the original compound patent on ipratropium granted in 1970, has therefore had patent protection in one form or another on this medicine for 58 years and counting (from 1970-2028).

Without a limit to long patent exclusivities, originators may be able to increase prices without consequences in the absence of competition. They may also be able to progressively phase out old delivery device models, forcing consumers to buy the new and more expensive ones, as has been observed in the media (6). For example, each one of Novo Nordisk's line of insulin aspart pens (Novolog Penfill®, Novolog Flexpen®, Novolog Flextouch®) contains a new mechanical feature. In principle, and possibly in fact, the Penfill® model can be phased out and a new one introduced, even if there was no therapeutic lack of efficacy with the Penfill®. In extreme cases, prices may be raised for trivial device improvements with no clinical value. One must wonder whether the health system should absorb the costs that it took to develop a novel "inhaler cap strap" (US patent 8387615) or other similar minor modifications (19).

These considerations are especially urgent considering that many of the 49 combination products are already top sellers in the United States with sales climbing annually. There are three studies referenced by the US National Library of Medicine for pharmaceutical statistics that ranked the top 100 or top 200 drugs by sales (20). More than one-third (n=17) of the 49 products examined by this study appeared one or more of those top seller lists (21-23). Of these, patent protection has been extended through the device in all cases with only a single exception (see Table 7.7.2). Figure 7.9.2 shows the steady increase of sales from 2011-2013 for the 8 products for which these data were available.

Given that the patent system is not likely to change much, whether because of tradition, the political influence of the pharmaceutical industry, or international framework treaties that lay down core requirements for patentability, how should the health system respond to potentially abusive evergreening?

Obviously, the first step is to be alert that device evergreening happens. This paper offers some evidence, but the practice is more widespread than recognized in the FDA

Orange Book (hence this paper did not look at insulin pumps, probes, continuous glucose monitors, and other devices which fall outside the Orange Book). One solution would be for FDA to introduce a companion or appendix to the Orange Book which records patents for broader categories of devices that are specifically approved for use with certain medicines (which would capture insulin pumps, for example) or that are part of an integrated system (such as glucose monitors whose software is part of a specific infusion pump). There is probably also scope to apply antitrust law, which prohibits “tied” sales, to the selling of specific medicines only with specific devices, as was done when the Federal Trade Commission prosecuted a pharmaceutical firm for tying its medicine to a specific blood test (24, 25). Without measures such as these, it falls to health technology assessment and insurance authorities to require suppliers to defend their choice of device technology before making reimbursement decisions.

7.7 References

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7.7 Tables

Table 7.7.1 – Drug/device combination products compared by patent type (device or medicament) and last patent expiration

Product	Active Ingredient	Device patent count	Non-device patents count	Proportion of device versus medicine patents	Last medicine patent expiration*	Last device patent expiration*	Patent protection added by device patent (in years)**	Number of suppliers of a marketed equivalent (brand or generic)***	Outcome typology****
COPD INHALERS									
Tudorza Pressair	ACLIDINIUM BROMIDE	3	4	43%	07-Aug-22	22-Apr-27	4.7	1	Device extension
ProAir HFA	ALBUTEROL SULFATE	2	3	40%	12-Sep-23	07-Sep-28	5.0	3	Device extension
ProAir Respiclick	ALBUTEROL SULFATE	8	0	100%	n/a	26-Mar-28	12.6	1	Only device patents
Proventil HFA	ALBUTEROL SULFATE	2	0	100%	n/a	28-Dec-16	1.4	3	Only device patents
Ventolin HFA	ALBUTEROL SULFATE	15	2	88%	01-Dec-21	19-Dec-23	2.0	3	Device extension
Combivent Respimat	ALBUTEROL SULFATE; IPRATROPIUM BROMIDE	17	0	100%	n/a	13-Mar-28	12.6	1	Only device patents
Duoneb	ALBUTEROL SULFATE; IPRATROPIUM BROMIDE	1	0	100%	n/a	28-Dec-21	6.4	6	Only device patents
Brovana	ARFORMOTEROL TARTRATE	0	12	0%	09-Nov-21	n/a	n/a	1	No device patents
QVAR	BECLOMETHASONE DIPROPIONATE	2	1	67%	07-Jul-15	13-Mar-18	2.7	1	Device extension
Pulmicort Flexhaler	BUDESONIDE	4	0	100%	n/a	08-May-18	2.7	1	Only device patents
Symbicort Turbuhaler	BUDESONIDE; FORMOTEROL FUMARATE DIHYDRATE	8	4	67%	29-Jan-23	07-Apr-29	6.2	1	Device extension
Alvesco	CICLESONIDE	2	5	29%	13-May-18	28-Dec-16	n/a	1	Old device
Aerospan HFA	FLUNISOLIDE	0	1	0%	07-Jul-15	n/a	n/a	1	No device patents
Breo Ellipta	FLUTICASONE FUROATE; VILANTEROL TRIFENATATE	7	7	50%	03-Aug-21	11-Oct-30	9.2	1	Device extension
Flovent Diskus	FLUTICASONE PROPIONATE	2	0	100%	n/a	23-Aug-16	1.0	1	Only device patents
Flovent HFA	FLUTICASONE PROPIONATE	16	2	89%	01-Dec-21	26-Aug-26	4.7	1	Device extension
Advair Diskus	FLUTICASONE PROPIONATE; SALMETEROL XINAFOATE	1	0	100%	n/a	23-Aug-16	1.0	1	Only device patents
Advair HFA	FLUTICASONE PROPIONATE; SALMETEROL XINAFOATE	16	2	89%	01-Dec-21	26-Aug-26	4.7	1	Device extension
Foradil	FORMOTEROL FUMARATE	2	0	100%	n/a	28-Nov-20	9.2	1	Only device patents
Perforomist	FORMOTEROL FUMARATE	0	5	0%	22-Jun-21	n/a	n/a	1	No device patents
Dulera	FORMOTEROL FUMARATE; MOMETASONE FUROATE	0	5	0%	21-May-20	n/a	n/a	1	No device patents
Arcapta Neohaler	INDACATEROL MALEATE	1	3	25%	10-Oct-20	11-Oct-28	8.0	1	Device extension
Atrovent HFA	IPRATROPIUM BROMIDE	3	2	60%	04-Nov-14	17-Jan-30	15.2	1	Device extension
Xopenex	LEVALBUTEROL TARTRATE	1	2	33%	08-Oct-24	17-Nov-15	n/a	1	Old device
Asmanex	MOMETASONE FUROATE	0	4	0%	27-Aug-17	n/a	n/a	1	No device patents
Asmanex Twisthaler	MOMETASONE FUROATE	4	7	36%	17-Sep-18	20-Aug-17	n/a	1	Old device

Striverdi Respimat	OLODATEROL HYDROCHLORIDE	16	7	70%	12-May-25	13-Mar-28	2.8	1	Device extension
Serevent Diskus	SALMETEROL XINAFOATE	1	0	100%	n/a	23-Aug-16	1.0	1	Only device patents
Spiriva	TIOTROPIUM BROMIDE	1	9	10%	22-Jan-22	12-Mar-27	5.1	1	Device extension
Spiriva Respimat	TIOTROPIUM BROMIDE	16	1	94%	30-Jan-18	13-Mar-28	10.1	1	Device extension
Incruse Ellipta	UMECLIDINIUM BROMIDE	6	4	60%	27-Jul-25	11-Oct-30	5.2	1	Device extension
Anoro Ellipta	UMECLIDINIUM BROMIDE; VILANTEROL TRIFENATATE	7	6	54%	27-Jul-25	11-Oct-30	5.2	1	Device extension
EPINEPHRINE PENS									
AUVI-Q	EPINEPHRINE	17	0	100%	n/a	02-Nov-29	14.2	2	Only device patents
Epipen	EPINEPHRINE	4	0	100%	n/a	11-Sep-25	10.1	1	Only device patents
Twinject	EPINEPHRINE	2	0	100%	n/a	04-Feb-25	9.5	2	Only device patents
INSULIN PENS									
Novolog Penfill	INSULIN ASPART RECOMBINANT	3	2	60%	20-Dec-17	02-Jun-15	n/a	1	Old device
Novolog Flexpen	INSULIN ASPART RECOMBINANT	3	2	60%	20-Dec-17	21-Jul-21	3.6	1	Device extension
Novolog Flextouch	INSULIN ASPART RECOMBINANT	5	2	71%	20-Dec-17	03-Aug-26	8.6	1	Device extension
Novolog mix Flexpen	INSULIN ASPART PROTAMINE; INSULIN ASPART	3	2	60%	19-Dec-17	21-Jan-21	3.1	1	Device extension
Lantus	INSULIN GLARGINE RECOMBINANT	1	3	25%	23-Jan-24	23-Mar-28	4.2	1	Device extension
Lantus Solostar	INSULIN GLARGINE RECOMBINANT	6	0	100%	23-Jan-24	12-Apr-25	1.2	1	Device extension
Toujeo Solostar	INSULIN GLARGINE RECOMBINANT	7	0	100%	23-Jan-24	23-Mar-28	4.2	1	Device extension
Apidra Solostar	INSULIN GLULISINE RECOMBINANT	7	4	64%	19-Dec-17	23-Sep-27	9.8	1	Device extension
Humalog Kwikpen 100	INSULIN LISPRO RECOMBINANT	1	0	100%	n/a	09-Aug-24	9.0	1	Only device patents
Humalog Kwikpen 200	INSULIN LISPRO RECOMBINANT	1	2	33%	11-Jun-18	09-Aug-24	6.2	1	Device extension
Humalog mix Kwikpen	INSULIN LISPRO PROTAMINE; INSULIN LISPRO	1	0	100%	n/a	09-Aug-24	9.0	1	Only device patents
Afrezza 4	INSULIN RECOMBINANT HUMAN	10	21	32%	08-Mar-31	12-Jul-32	1.3	1	Device extension
Afrezza 8	INSULIN RECOMBINANT HUMAN	9	19	32%	08-Mar-31	12-Jul-32	1.3	1	Device extension
Afrezza 12	INSULIN RECOMBINANT HUMAN	10	14	42%	11-Jun-30	12-Jul-32	2.1	1	Device extension

* Paediatric and other patent extensions are included whenever relevant.

** For medicines listing no patent on the active ingredient, only device patents were listed. We used August 15, 2015 (the date of accessing the database) as the baseline.

***Equivalents were defined as those delivering the identical medicament, strength, (co-)formulation, and route of administration

****"Device extension" means the last-to-expire device patent was after that of the last-to-expire formulation patent; "Only device patents" means that only device patents remain unexpired and that all patents of any other type have expired; "Old device" means the last-to-expire patent on the formulation was after that of the last-to-expire device patent; and "No device patents" means that no unexpired device patents were listed. Only patents on the formulation remain unexpired

Table 7.7.2 – Top-Selling Drug/device combination products with device extension outcomes

Product	Active Ingredient	Supplier	Rank in Top 200 by Sales by Pharmacy Times (2012)	Rank in Top-100 Drugs by Sales by Drugs.com (2013)	On Top 200 Drugs by Sales by RxList (2015)	% of device patents in portfolio	Last medicine patent expiration*	Last device patent expiration*	Outcome typology**
<u>COPD INHALERS</u>									
ProAir HFA	ALBUTEROL SULFATE	TEVA BRANDED PHARM	53	41	X	40%	12-Sep-23	07-Sep-28	Device extension
Ventolin HFA	ALBUTEROL SULFATE	GLAXOSMITHKLINE	93	95	X	88%	01-Dec-21	19-Dec-23	Device extension
Combivent Respimat	ALBUTEROL SULFATE; IPRATROPIUM BROMIDE	BOEHRINGER INGELHEIM	51	83		100%	15-Aug-15	13-Mar-28	Only device patents
QVAR	BECLOMETHASONE DIPROPIONATE	TEVA BRANDED PHARM	170			67%	07-Jul-15	13-Mar-18	Device extension
Symbicort Turbuhaler	BUDESONIDE; FORMOTEROL FUMARATE DIHYDRATE	ASTRAZENECA	43	31	X	67%	29-Jan-23	07-Apr-29	Device extension
Flovent HFA	FLUTICASONE PROPIONATE	GLAXO GRP LTD	60	58	X	89%	01-Dec-21	26-Aug-26	Device extension
Advair Diskus	FLUTICASONE PROPIONATE; SALMETEROL XINAFOATE	GLAXO GRP LTD	4	5	X	100%	15-Aug-15	23-Aug-16	Only device patents
Advair HFA	FLUTICASONE PROPIONATE; SALMETEROL XINAFOATE	GLAXO GRP LTD	186			89%	01-Dec-21	26-Aug-26	Device extension
Xopenex	LEVALBUTEROL TARTRATE	SUNOVION			X	33%	08-Oct-24	17-Nov-15	Old device
Spiriva	TIOTROPIUM BROMIDE	BOEHRINGER INGELHEIM	15	13	X	10%	22-Jan-22	12-Mar-27	Device extension
<u>EPINEPHRINE PENS</u>									
Epipen	EPINEPHRINE	MYLAN SPECLT	139			100%	15-Aug-15	11-Sep-25	Only device patents
<u>INSULIN PENS</u>									
Novolog Flexpen	INSULIN ASPART RECOMBINANT	NOVO NORDISK INC	57	34		60%	20-Dec-17	21-Jul-21	Device extension
Novolog mix Flexpen	INSULIN ASPART PROTAMINE; INSULIN ASPART	NOVO NORDISK INC	168			60%	19-Dec-17	21-Jan-21	Device extension
Lantus	INSULIN GLARGINE RECOMBINANT	SANOFI AVENTIS US	19	16	X	25%	23-Jan-24	23-Mar-28	Device extension
Lantus Solostar	INSULIN GLARGINE RECOMBINANT	SANOFI AVENTIS US	21	11	X	100%	23-Jan-24	12-Apr-25	Device extension
Humalog Kwikpen 100	INSULIN LISPRO RECOMBINANT	LILLY	98	69	X	100%	15-Aug-15	09-Aug-24	Only device patents
Humalog Kwikpen 200	INSULIN LISPRO RECOMBINANT	ELI LILLY AND CO	98	69	X	33%	11-Jun-18	09-Aug-24	Device extension

* Pediatric and other patent extensions are included whenever relevant

**"Device extension" means the last-to-expire device patent was after that of the last-to-expire formulation patent; "Only device patents" means that only device patents remain unexpired and that all patents of any other type have expired; "Old device" means the last-to-expire patent on the formulation was after that of the last-to-expire device patent; and "No device patents" means that no unexpired device patents were listed. Only patents on the formulation remain unexpired

7.8 Figures

Figure 7.8.1 – Last-to-expire device patent versus medicine patent comparative analysis outcomes

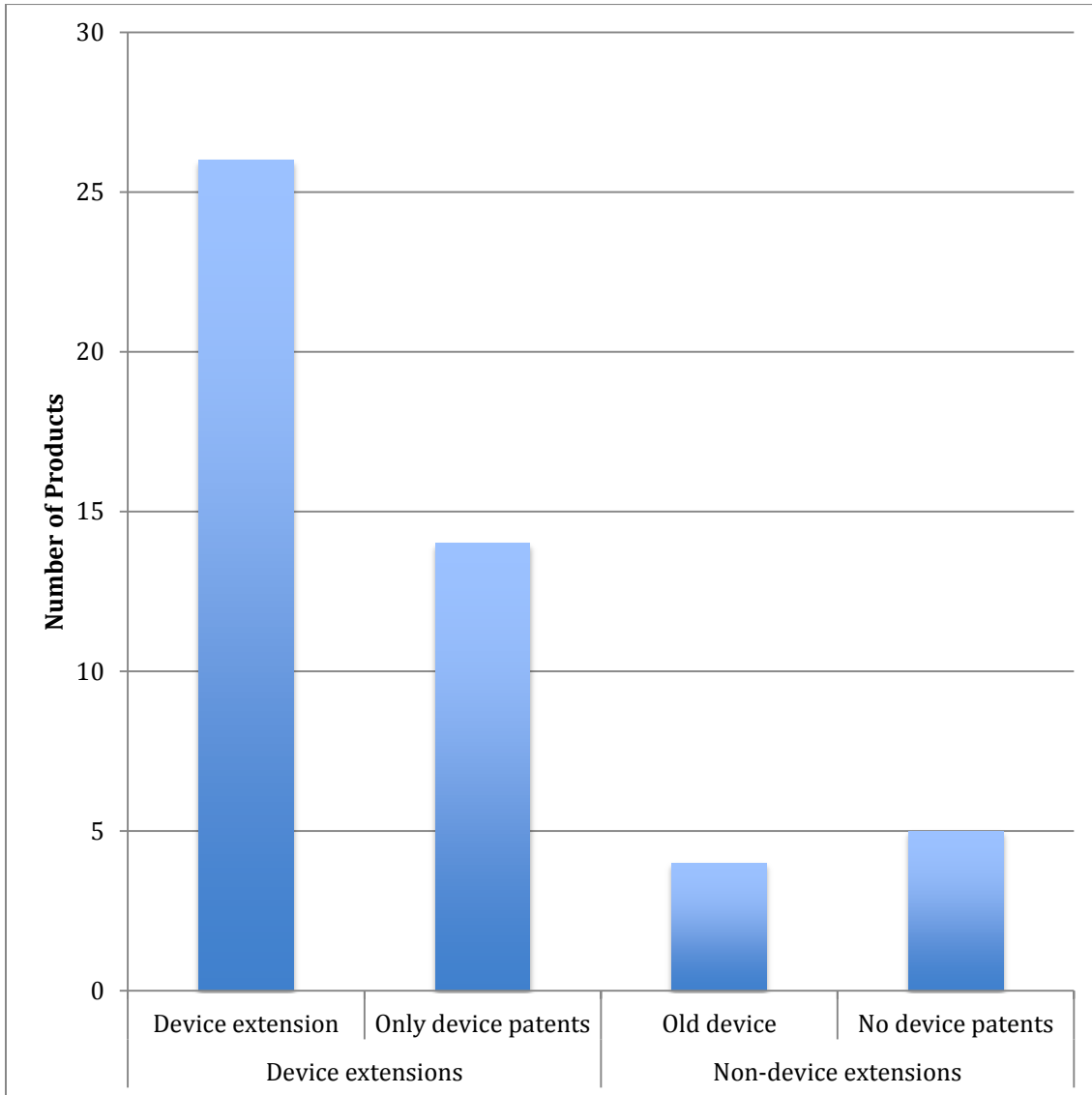
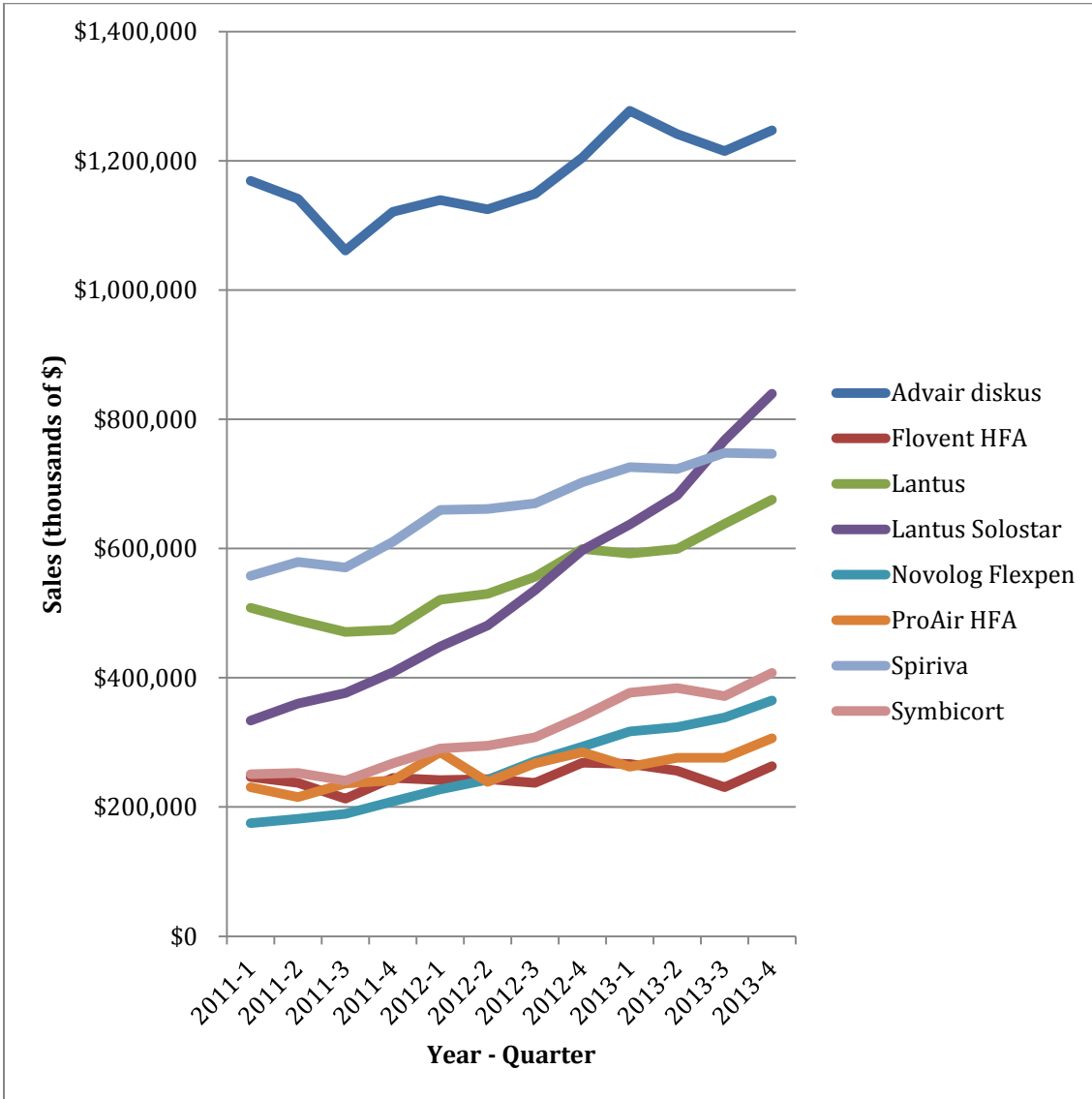


Figure 7.8.2 – Sales for 8 medication-device combination products in 100-top sellers in the US from 2011-2013 (22)



Conclusion

This dissertation project has discussed the nature of patent filing activity on medicines internationally, and its potential implications for policy and medicine access in developing countries. None of its investigations would have been possible without some level of medicine patent transparency. Given that the essential medicine patent landscape will continue to evolve along with our world's changing demographic and epidemiologic profiles, it is imperative that investigations like these continue. Therefore, while this thesis project has several implications for research and policy, its most important recommendation is also its most foundational and basic one encapsulated by Chapter 2 (Article 1) (1)—namely, the call for international medicine patent transparency by multinational pharmaceutical companies, and, ideally, for the eventual creation of a centralized international medicine patent register.

Accordingly, this concluding chapter focuses upon the transparency issue. It summarizes some lessons learned about its importance within the context of this dissertations' other chapters, documents key knowledge translation activities in policy environments undertaken during the period of study, summarizes next steps going forward, and finally reflects upon what has been learning through completing this research, both for population health and for access to medicines.

8.1 Summary of thesis findings and implications regarding patent transparency

Our research has found that while the majority of patents on MLEM products have expired, there is nevertheless a subset of drugs for which patents are indeed in force in some developing countries, as was discussed in Chapter 3 (Article 2) (2-4). Besides patents on the active ingredients, companies continue to redevelop and re-patent products long after the expiration of the primary patents on the compound, as was demonstrated by Chapter 6 (Article 5) (5) and Chapter 7 (Article 6) (6). Some of these new (co-) formulations

are of great interest to global public health and are not simply cases of “evergreening.” Further, there is good reason to suspect that more patented products will be added to the MLEM in the future than has previously been the case, as was argued in Chapter 3 (Article 2) and the WIPO report (2-4). Chapter 3 (Article 2) (3) and Chapter 4 (Article 3) (7) show that just a few essential medicine patents can be positioned to have large impact upon access to particular medicines across developing countries. Thus, there are indeed specific cases in which patents could heavily influence essential medicine access and these should receive proportionate policy attention. A critical activity, then, is identifying these specific cases where patenting may be a critical issue.

Unfortunately, the fundamental task of isolating these key essential medicine patents and determining their current legal status internationally can be exceedingly difficult for third parties. This matter was discussed at length in Chapter 2 (Article 1) (1). What is retrieved by third parties from international patent databases is dated, may be irrelevant, and is influenced by the variety of methodologies and databases available. Dead patent records commonly appear to be active in international patent databases, which misrepresents and inflates third party estimations of the territories covered by a given medicine’s patent portfolio. There is much room for error. The implication is that it is only the individual companies who know the current status of their patent applications globally and which ones they intend to enforce. What is known collectively, therefore, about patenting activity on all (essential) medicines globally at any given time is necessarily fragmented, inaccurate, and/or outdated.

As was also discussed in Chapter 2 (Article 1) (1), this fundamental deficiency in global medicine patent surveillance is problematic for different stakeholders for different reasons, and accordingly impacts medicine access from many angles. For example, it affects international medicine procurement officers, importers, exporters, and generic competitors

(8). These stakeholders use patent information to determine where they have legal freedom to operate, to avoid patent infringement, and to maximize value for dollar when making buying or selling decisions (9). False or ambiguous patent information can misinform or unnecessarily complicate and delay these decisions. Procurements are postponed to allow time for legal consultation and budgets are diminished in order to pay for such advice (10). Further, the lack of sound data also introduces considerable unknowns to the policy debate on access to medicines vis-à-vis patent protection and allows for discourses and rhetoric to become disconnected from empirical reality (1). Policy interventions based on imperfect information are likely to lead to suboptimal results or unintended consequences. Therefore, the inaccessibility of international medicine patent information inhibits the everyday work of global health actors and generates inefficiencies that have real consequences on medicines access.

In sum, the status quo is one in which the true global medicine patent situation is known only in part by a select few. Such a status quo has not been tolerated at the national level in countries like the United States and Canada. Both countries established national medicine patent registers in part to improve the accessibility of this important information. Something similar should exist at the international level.

Besides counteracting the aforementioned inefficiencies, maintaining this current state of affairs also comes at an enormous opportunity cost for global public health. The increased visibility upon companies' international patent holdings will also increase the potential for criticism for holding patents in developing countries from civil society, for the validity of key patents to be challenged, and for compulsory licenses to be issued. To prevent such contingencies (e.g., compulsory licenses), companies can proactively make heavier use of the variety of policy options available (e.g., voluntary licensing, tiered pricing, non-assert policies), which they developed during the global campaign for HIV medicine

access as was discussed in Chapter 4 (Article 3) (7). It is no coincidence that GlaxoSmithKline's recent announcement about expanding their use of these policies has been done in parallel with increasing the company's patent transparency (11). Indeed, our research has shown that while patents can serve as barriers to medicine access, they can also serve as springboards for access campaigns and technology transfer via voluntary licenses to generic pharmaceutical companies based in developing countries. Chapter 4 (Article 3) (7) has demonstrated that, at least within the context of the global campaign for HIV medicines, generic competition might be more common where there is a patent presence (either in the exporting country and/or importing country) than where there is none whatsoever. Chapter 5 (Article 4) (12) has shown that cooperative approaches (e.g., voluntary licenses) can produce prices that are comparable or better than those of compulsory-licensed prices. Increased patent transparency would likely foster more of all of these positive activities.

These are only a few reasons why improving the accessibility of international medicine patent information will foster greater accountability, licensing activity, technology transfers, access campaigns, and ultimately accessibility to new essential medicines at the international level. Therefore, advocating for international medicine transparency by supplier companies and for an international medicine patent register became a particular emphasis in this project's knowledge translation activities and actions during the period of study.

8.2 Actions taken to promote international medicine patent transparency

Population health is an action-oriented field (13). This means that the publication of research findings is not where the researcher's role ends, but is instead the beginning of another process in which the objective is to inform policy with one's research findings in order to advance population health and health equity (14). One way in which this can be

built into a research program is through an iterative research-action cycle, i.e., as the researcher gains additional experience about the subject of study through engaging stakeholders to inform policy decisions with research findings, this experience can then be leveraged to glean new insights to further refine the research program and make it more useful to knowledge users and more effective at stimulating positive change (15, 16).

Examples of formalized versions of these practices within health research are “knowledge translation” (17), the “knowledge-to-action cycle” (18), and “action research” (19). In this spirit, therefore, aside from the usual procedures to disseminate research findings through purposefully selected peer-review journals and academic conferences, three main efforts in particular were undertaken to engage key stakeholders groups in policy environments during the course of study. These efforts to get international medicine patent transparency on the international policy agenda (20) are detailed below along with some reflections for future iterations of the research-action cycle.

8.2.1 Presentation at the Trilateral Meeting of the WHO, WTO, and WIPO

The first of these efforts was to present research findings at the Joint Technical Symposium of the WHO, WTO, and WIPO in Geneva on 28 October 2015 (21). The subject of the meeting was “Public Health, Intellectual Property, and TRIPS at 20: Innovation and Access to Medicines; Learning from the Past, Illuminating the Future.” The topic of the panel was “Ongoing Health Challenges and Policy Responses: What Do the Data Say?” The message of my presentation was that the poor availability of quality patent data inhibits attempts to determine what the data actually say, and that with better data availability, many lessons can be learned to steer policies in more productive directions. As the invitation to speak came as a result of the publication of Chapter 5 in *Health Affairs* (12) and subsequent debates in its Letters to the Editor Section (22, 23), this article was used as an example of the kind of lessons that may be learned through access to patent and

procurement data, namely, that while the literature has largely focused upon compulsory licensing as a way of reducing medicine prices, cooperative approaches (e.g., voluntary licensing) could actually produce similar or even better results. While the message of Chapter 5 (Article 4) was debated, there was unanimous agreement amongst the panelists upon the negative impact of poor patent data upon medicine access and the importance of international medicine patent transparency (21). (The other panelists were Peter Beyer, a senior advisor on the subject to the WHO; Cornelis De Joncheere, the Director of the WHO's Department of Essential Medicines and Health Products; and Ellen 't Hoen, an internationally known author who was the first Executive Director of the Medicines Patent Pool).

There were two major outcomes from this meeting for this research project. First, the fundamental policy recommendation of this project regarding patent information was validated by key informants during a meeting of significant international importance. Second, several important challenges were identified, albeit during informal encounters with key persons during trilateral meetings. Several policy advisors reported that while the argument for transparency had been made previously, its connection to medicine access had not yet been done in a compelling fashion. They reported that some stakeholders had expressed skepticism that the amount of effort required to set up an international medicine patent register would not be proportionate to the public health impact, and therefore, the idea had been falling to the bottom of the policy agenda for over 15 years in favor of pursuing more radical policy solutions. Finally, several representatives from pharmaceutical companies repeatedly noted that patent information is a part of public record, and therefore, those who need the information (i.e., professional medicine patent lawyers) will have no trouble finding it. Going forward, therefore, it was clear that (i) the argument for the practice of voluntary international patent transparency from companies

needed to be further crystalized and that (ii) the public health community needed to better document wide and clear consensus on the matter.

8.2.2 The United Nations Secretary-General's High-level Panel on Access to Medicines

In November 2015, the United Nations Secretary-General announced the formation of a High-level Panel (UNHLP) on the subject of access to medicines and made a call for written contributions, including matters related to intellectual property protection (24). After making substantial improvements to the manuscript that is now Chapter 2 (Article 1), it was submitted to the UNHLP under the title “(In)accuracy of using US and Canadian patent registers for determining medicines' patent status globally: A call for global patent transparency on essential and lifesaving medicines” (25). The paper was selected for an oral testimony in front of the UNHLP and its Expert Advisory Group on 9 March 2016 in London, England (26). My brief opening statement argued that available international patent databases are insufficient for delivering reasonably accurate and reliable medicine patent status information and that the UNHLP's first and most basic demand ought to be for a clear and accurate picture of the global medicine patent landscape; the speech ended by urging the UNHLP to build and demonstrate consensus on the matter and to urge supplier companies to practice international medicine patent transparency voluntarily in the name of public health.

The second day of the HLP summit was a town hall style meeting called the “Global Dialogue” (27). Attendees included a variety of stakeholder groups, such as representatives from pharmaceutical companies (e.g., Novartis, GlaxoSmithKline), from access to medicines activist groups and civil society (e.g., Médecins Sans Frontières (MSF), Knowledge Ecology International (KEI)), from academic institutions (e.g., Harvard University, London School of Economics), from international organizations (e.g., the WHO, WIPO), and from national government entities (e.g., United States Department of Commerce, the United Kingdoms’

National Institute for Health and Care Excellence (NICE)). The dialogue was facilitated by Andrew Jack of the Financial Times. Once the dialogue began, it was apparent that there was a deep ideological divide amongst the attendees regarding the causes and nature of the access to medicines problem in developing countries. I attempted to intervene, arguing that many of these fundamental questions could be answered empirically if proper data were available. I proposed voluntary international medicine patent transparency as the most immediate solution and an international medicine patent register as a longer-term solution for breaking the ideological logjam that appeared to be preventing cooperation between stakeholders.

Whether the UNHLP will adopt this suggestion remains to be seen. The HLP report is not yet available, but is due to be published this summer (2016). The ideal outcome would be that the UNHLP report documents consensus on the transparency issue and/or the need for an international medicine patent register. Transparency (including on patent transparency) was a common thread of the testimonies before the UNHLP. Mr. Andrew Witty, the CEO of GlaxoSmithKline, is a member of the UNHLP (28). A few weeks after the meeting, he and his company announced their intent to disclose information on their global patent holdings and to expand their voluntary licensing agreements (11). His actions may suggest that he is anticipating that the UNHLP's recommendations will indeed include the subject of international medicine patent transparency. Mr. Witty was apparently receptive to the testimonies at the London meeting, and his company has set a progressive example of company policies to promote access to medicines internationally. Regardless of what the UNHLP report says, one success of this research project was contributing to those messages heard by Mr. Witty at the UNHLP summit that compelled him to adjust his company's policy.

Upon reflecting on this experience, next knowledge translation steps would include using GlaxoSmithKline's example to encourage other companies to follow suit, to continue

to further crystalize the case for patent transparency, to remain steadfast in pressing it as a viable policy option, and to work towards documenting consensus on the matter from the global public health community.

8.2.3 WIPO Global Challenges Seminar

The third major knowledge translation activity was the Global Challenges Seminar on 12 April 2016 in Geneva (29). This meeting was scheduled to promote the publication release of the WIPO report (2, 4), the data from which serves as the basis for Chapters 2-4 (Articles 1-3) (1, 3, 7). The seminar was well-attended by members of key institutions based in Geneva, including international organizations (e.g., WHO, WTO) and civil society (e.g., MSF, KEI). My opening statement (30) provided an explanation for why reports like these are necessary, namely, that while medicine patents are technically part of public record, the task of identifying key patents and determining their current legal status globally is impossible for third parties to perform with a reasonable level of speed, reliability, and accuracy. After summarizing the study results, the presentation closed with highlighting the role of transparency by companies, of the ultimate need for a global medicine patent register, and of the public health community to be more active in demanding these things.

The WHO, MSF, and KEI in particular took offence at the suggestion that the global public health community had not been active enough in demanding medicine patent transparency. They referenced many other patent studies by third parties that had been done for specific medicines, which from our perspective was irrelevant. In retrospect, the disagreement centered upon what is meant by “international medicine patent transparency.” When our report referred to “international medicine patent transparency”, we were recommending that it ought to be common practice for companies to voluntarily disclose information to the public about their current international patent holdings, such as by posting it on their website. Our WIPO report (2, 4) referenced to the study described in

Chapter 2 (Article 1) (1) and made this recommendation based on the discrepancy between the results of third party patent studies and companies' records, stating that the implication that it is "only patent holders themselves [who] truly have an accurate picture of their patent holdings" (2). Therefore, while third parties may have published several medicine patent studies of high-quality that identify essential medicine patents held by others, this is no substitute for company disclosures of their own records on their own international patent holdings. Our concern was that the public health community had not yet demonstrated wide consensus on this matter and has not yet shown a sustained and routine demand for it over the years.

I contacted the WHO, MSF, and KEI to clarify what we meant by international medicine patent transparency in the WIPO report. I invited them to co-author a letter on the topic to document and foster consensus. The letter would define what is meant by international medicine patent transparency, detail exactly what information companies practicing such transparency would ideally make publicly available, and briefly summarize some reasons why such a practice is so important. All three organizations declined the invitation on the grounds that there were political reasons why their organizations could not participate and/or repeated that they had already been doing much work on the transparency issue and would continue to do so (31). Even though the matter had been clarified, KEI later disregarded this correspondence and instead published an article on their website that reiterates the original misunderstanding from the WIPO meeting; ironically, this post is the organization's first page devoted explicitly and specifically to international medicine patent transparency (32). It was clear that the politics of the situation were so deeply rooted that even when stakeholder groups agreed on specific matters, many are still unwilling to be seen working together, even in the name of public health. Further, it is quite possible that there is not yet a clear and wide consensus within

the global public health community about what the role of pharmaceutical companies is in improving access to patented medicines in developing countries and whether voluntary international medicine patent transparency by companies could or should be a vital component. For example, MSF's representative at the WIPO meeting, Yuanqiong Hu, argued that our WIPO report was corrupt because we had worked with companies to validate our data (29); the implication is that patent information voluntarily disclosed by companies simply cannot be trusted.

Unrelated to this misunderstanding with groups from civil society, several individuals from African patent offices approached me after the presentation. They explained that if they had more resources and training, their increased capacity would dramatically improve the accessibility of the medicine patent information available from their countries. They wanted to know how to best advocate for more resources for their offices. Certainly, building the capacity of patent offices in developing countries would be a tremendous service. Others have described how these offices' responsibilities were often increased in order to meet trade agreement obligations without the foresight of identifying where the necessary additional resources would come from for such capacity building (58). WIPO is aware of these challenges, and it is evident in its development agenda (59). How exactly these challenges are best overcome is a debatable subject that requires further study and is not covered in this thesis. It may be a fruitful area of research for postdoctoral study or other investigations in the future.

8.3 Future research and action in international medicine patent transparency

As of writing, the events described above following the WIPO meeting transpired within the last few months. This section describes some actions going forward, which would be productive next steps in advancing international patent transparency and/or the creation of an international medicine patent register. These are described below and

include (i) the publication of case studies to illustrate how the lack of patent information interferes with the daily work of medicine procurement officers and policymakers, (ii) the publication of a brief statement by key actors in the public health community that would document wide consensus on the issue, and finally, (iii) use of the information gathered through these first two items to push for international medicine patent transparency to be on the agenda of the World Health Assembly (WHA) in 2017.

8.3.1 Case studies investigating the consequences of deficient international medicine patent information

This thesis has discussed some of the problems that arise due to the lack of sound international medicine patent status information. There are a few publications (10), including one qualitative survey of key informants (9), which document that the lack of patent information can misinform and/or delay procurement and policymaking activities. But there remains a lack of rigorous qualitative case studies investigating exactly how this interferes with the everyday activities of personnel working on drug access at the international level. If such a study documented substantial interference, it would add tremendous weight to the argument for international medicine patent transparency and a register. The biggest challenge with conducting such a study, however, is getting procurement officers, policymakers, and other key informants to agree to participate in formal interviews.

8.3.2 Consensus statement by key actors in the public health community on patent transparency

As mentioned above, there is a critical need for a one-page consensus statement that is devoted specifically to the subject of transparency. A draft example of such a document is included in Appendix 8.1. It defines international medicine patent transparency and asks for companies to practice it in the name of public health. It explains why such transparency is

important and asks for the matter to be on the agenda of the WHA. Such a letter would have been of great service when we were conducting the WIPO study, as many companies were reluctant. Even though such transparency is consistent with WIPO's Intellectual Property Development Agenda (59), a statement from the public health community would be extremely useful. If published, researchers can reference this document in the future when approaching companies for patent data. Even if the WHO alone made an official statement specifically about the importance of patent transparency by companies, it would be extremely useful for eliciting cooperation from companies and other key actors. Once the UNHLP report is available and once Chapter 2 (Article 1) is published, these occasions can be leveraged to attempt again to obtain the cooperation of key actors in the public health community to co-author the consensus statement. The primary challenge with this approach is that the same political reasons for certain key actors' non-participation will still remain. However, the publication of the full concordance study (Chapter 2/Article 1) may further clarify the argument of the WIPO report (2, 4) and resolve the some misunderstanding evident at the Geneva meeting and in the responses from the WHO, KEI, and MSF. Further, should the UNHLP report mention the matter of transparency in its recommendations, it will likely alter the political environment as many global public health actors are more willing to act upon recommendations coming from this panel, which is a political entity, rather than from academic observers outside of this group.

8.3.3 A WHA resolution on international medicine patent transparency and/or an international medicine patent register

A WHA (33) resolution would be the most powerful and effective demonstration of consensus on the subject of patent transparency possible because the countries that comprise the WHA are home to the pharmaceutical industry's markets. Getting on the agenda of the WHA is no easy task, however. With the aforementioned items in place, the

publications can be sent to the WHO with a cover letter urging them to add patent transparency to the agenda. Indeed, much of the groundwork towards getting on the WHA agenda can be achieved through the aforementioned creation and revision of the consensus statement document.

8.4 Reflexive anthropological and theoretical reflections on population health, access to medicines, and patent transparency

8.4.1 Population health theory and access to medicines

Returning to the theoretical matters discussed in this dissertation's Introduction, there are many social determinants of health in multiple sectors, at multiple levels, both upstream and downstream, which interact and shape the inequitable health disparities that have been observed between population groups that differ socioeconomically. As has been conceptualized in Figure 1.9.1, the health system is a downstream social determinant of health; and as such, it is in the unique position of mitigating health inequities or reinforcing them by offering health-restoring services differentially across socioeconomic groups. The latter is the current state of affairs reflected in today's global society, i.e., those who need medical attention the most are often the last to get it (i.e., the inverse care law).

A critical input into the health system is medicines. This project has investigated the assertion that one contributing factor to reinforcing the inverse care law in the health sector is the patent system's integral role in funding modern pharmaceutical R&D. There is sound theoretical reasoning to suspect that this reinforcement could indeed be the case (especially within commercial environments without universal health coverage) since it incentivizes R&D that benefits already advantaged populations and gives them priority access to those novel medications.

Whether this is norm today and whether medicine patent protection contributes substantially to population-level health differences between countries, however, is less

clear. Better international medicine patent and procurement data is necessary to study this question from a global public health perspective. Patent transparency by companies and/or an international medicine patent register would enable researchers to gain much more clarity on whether system-wide reform is needed at the international level and how the current system may be adapted to work better from an equity perspective.

8.4.2 The access to medicines ideological divide in history and today

Regardless of the story that larger datasets may tell, the history of the previous decade still remains influential. Several companies used the patent system to justify their exorbitant prices and countries like the United States have threatened to use trade sanctions against developing countries (e.g., South Africa, Brazil, Thailand) to serve the interests of multinational pharmaceutical firms (34-36). These cases have justifiably fuelled backlashes against the pharmaceutical industry and the patent system. Particularly in the early days of the global campaign for HIV medicines, there was a radical and aggressive agenda that resonated with the spirit of AIDS activism, such as the AIDS Coalition to Unleash Power (ACT UP), and with the ideological clashes that exploded at the 1999 Seattle WTO Protests (37). While this uncompromising posture contributed to achieving many positive changes, it also created a palpable rift that continues today between the pharmaceutical industry and many actors within civil society working on access to medicines.

Even though many access to medicines activist groups are now pushing a more incremental agenda of “delinkage” (38), I was struck when I attended the UNHLP Global Dialogue Meeting that this rift is still very much alive today (27). The meeting’s attendees were predominately skeptics of the patent system’s role in the pharmaceutical industry. The minority of attendees were proponents, wanting to recognize the successes of the patent system’s role and build upon them. When representatives from brand name drug companies and manufacturers’ associations spoke to the group about how the patent

system forms the backbone of their industry's R&D and business models, their viewpoints were typically met with laughter and disregard. The unwelcoming atmosphere in the room for these individuals was unmistakable. By mid-day, several of them had understandably excused themselves and began having their own discussion about medicine access programming in the hallway outside of the Global Dialogue Meeting Room. I found this saddening because drug-makers and innovators are undoubtedly one of the most important stakeholders to have at the table. Excluding their perspective is unlikely to result in optimal outcomes. Observing the ideological gulf about medicine patents manifest physically as these groups sorted themselves was a remarkable experience for me as a researcher in this area and has helped shape my perception of the field of access to medicines.

8.4.2.1 The access to medicines ideological divide: Stakeholder engagement and embedded determinants of health

This experience at the UNHLP (and other similar ones) has likely influenced some of the policy recommendations contained in this dissertation's articles (e.g., the interest in collaborative interventions), which aligned well with my theoretical background and training as a population health researcher. For example, stakeholder engagement is a principle within population health (39). This involves identifying and engaging the key institutions, organizations, and communities that influence the health outcome of interest (40-44). This process is critical for creating interventions that are tailored to the context and fit-for-purpose, and as such, are more likely to be taken up by the system and be mainstreamed (15, 16, 45-47). Complex systems include determinants that help maintain their overall structure. These determinants are embedded securely and deeply within them. Complex systems, therefore, will be especially resistant to considerable changes in these embedded determinants (48, 49). When it comes to access to medicines, the patent system's role may be one such embedded determinant. An approach for dealing with embedded

determinants is to retrofit them (rather than try to remove them entirely) so that they will work more favorably for health equity (at least until wider system change becomes possible). Cooperative voluntary patent licensing agreements between brand name companies and generic ones certainly seems to be an example of one such intervention because they appreciate patents' embedded role within the pharmaceutical industry's R&D and business models and accelerate generic drug access internationally. Voluntary licensing, therefore, is more likely to be adopted by these key stakeholders and positively impact equitable access in the real world.

8.4.2.2 The access to medicines ideological divide: The view from discourse analysis

Relatedly, with respect to factors that appeared to reinforce the schism between the pharmaceutical industry and other actors in access to medicines, there seemed to be an active discourse at play which demonizes brand name drug companies as patent-wielding profiteers without scruples and which idealizes other stakeholder groups, including generic pharmaceutical companies and civil society (who are portrayed as heroic) and developing countries' governments (who are portrayed as weak and vulnerable). Discourses are oversimplified narratives about groups of people that are socially constructed and perpetuated in the media, culture, and politics. Discourses can take root in fact, but can also take on a life of their own and become misleading or even dangerously wrong (50). While I have not yet conducted a formal discourse analysis on this access to medicines narrative (51, 52), I have informally observed its presence and influence in the literature throughout my PhD studies and believe that I have clashed with it periodically during my attempts at knowledge translation.

Discourses can be disrupted when facts are revealed that contradict the main narrative or when counter-discourses emerge (53-55). While I observed many elements of empirical truth in the access to medicines narrative, I also commonly observed facts that

clashed with it. For example, our WIPO report documented that the Indian generic pharmaceutical company Cipla filed for patents in Sub-Saharan Africa for their triple combination anti-retroviral therapy during the launch of the HIV campaign. This came as a shock because Cipla is a main actor in this discourse and in the history of the global campaign for HIV medicine access. I was naturally surprised when they repeatedly refused to participate in our essential medicines patent study with WIPO and instead gave us their “Never Say Die” pamphlet (56), which perpetuates their heroic role in the access to medicines discourse. The fact that Cipla was the only multinational pharmaceutical company to deny our requests for essential medicine patent transparency caused some cognitive dissonance for me. I found myself wondering if Cipla had remained obstinate precisely because they hold an extensive medicine patent estate in developing countries and the company feared a disruption in this discourse, which portrays them as heroic opponents of the patent system and which has been useful for their public image and business interests (since they often walk the line infringement to be the first to sell generic equivalents of brand name products).

When I began this research, I confess that I rarely questioned the access to medicines discourse; now after having interacted with variety of stakeholders on different sides of the issue, I am mindful that the situation is far more nuanced and complex than it is often portrayed (57). I believe it is important to challenge this discourse where appropriate. This desire to interrupt and reinvent the access to medicines narrative to be more accurate with empirical and historical reality may show through in the articles contained in this dissertation work and in related future works. The existence of the access to medicines discourse is yet another reason why international medicine patent transparency is a critical tool for keeping this powerful narrative as grounded as possible in empirical reality.

8.5 Overall conclusion

This dissertation project has investigated the nature of the essential medicine patent landscape in developing countries and how medicine access can be accelerated given the realities of the pharmaceutical industry and trade. The analysis of the data collected for this project has shown that while there are relatively few patents on essential medicines in developing countries, the patents that do exist may still have large potential to influence medicine access in those specific cases (e.g., hepatitis) and have a correspondingly large global health impact, but this influence might be positive as patents do not necessarily have to block competition and can even serve as springboards for technology transfer to developing countries and for global access campaigns, like the one for HIV. While this project has provided some insights to answer its main research question, it is only one snapshot in time of the global essential medicine patent landscape. It is imperative that it continue to be monitored as it evolves over the years as the MLEM is revised to meet the world's changing demographic and health needs. Patent transparency by pharmaceutical suppliers is critical to that end. Several efforts have been made during the period of study to advance this cause, including one that likely helped change at least one major global pharmaceutical supplier company's policy on the matter and will accelerate access to those products in developing countries (11). Future research and consensus building exercises stemming from this research program will hopefully persuade other companies to follow suit.

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8.6 Appendix – Draft consensus document: A call for international patent transparency on essential medicines from pharmaceutical companies

This letter is to document the request of pharmaceutical companies to practice international medicine patent transparency. More specifically, that they disclose information on their international patent holdings, particularly for products appearing on the World Health Organization's (WHO) Model List of Essential Medicines (MLEM) (1).

The MLEM is used for priority setting for global health actors working on medicine access. Many foundations and major charities base their drug procurement activities on this list. Medicine procurement officers and other global health actors working on medicine access at the international level need patent information to avoid patent infringement, and maximize value for dollar (2-4). Further, policy makers need the ability to direct interventions correctly to ensure that conflicts between patent protection and medicine access are addressed. Entities such as the United Nations Secretary General's High Level Panel on Access to Medicines, require a clear and accurate picture of the patent landscape of essential medicines for crafting policy recommendations at the international level (5).

Medicine patent information internationally is incredibly difficult to acquire with a reasonable level of speed and accuracy as a third party. Deciphering which patents are related to what products is difficult even in the United States and Canada where infrastructure and resources are relatively high; and in part to address this issue, both countries have instituted medicine patent registers (6, 7). Even when one uses these North American patent data to find related patents in other countries via international patent databases, the information is imprecise and lacks updated information on the patents' current legal status, causing one misestimate patent protection; only patent-holding companies have the most accurate information on which of their products are patented and where they intend to enforce those patents (8-10). The fundamental legal principle

underpinning the patent system is disclosure in exchange for market rights. This is an instance where disclosure is necessary at the international level, and where refraining from such disclosure has negative public health consequences.

The information ideally disclosed would include the patent and application numbers organized by patent family and would include the expiration dates (including extensions), current legal status, and the type of protection afforded (compound, process, etc.). Information on whether generic competition is present in a particular market would be assistive. Companies efforts to increase access to lower cost medicines in developing countries, such as commitments to refrain from enforcing patents in certain regions or licensing agreements with generic manufacturers is critical to include in the same place. While these records should be kept current, the time of the most recent update would be beneficial.

We urge companies to practice international medicine patent transparency for the sake global public health, and we urge the global public health community to push for this matter to be on the agenda of the next World Health Assembly. The authors of this letter come from a wide variety of stakeholder groups and have found the lack of transparency, as described here, to be disruptive and problematic in their daily work to improve medicine access at the international level. Companies such as GSK (11), Merck KGaA (12), and Novo Nordisk (13) have already committed to this practice and will accordingly score higher in the Access to Medicines Index (14). We hope more will follow. It stands to good reason that those benefiting from and advancing the medicine patent system should voluntarily do their part to be transparent about exactly where essential medicine access and patent protection might come into conflict and what they are doing address these concerns.

8.6.1 References

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