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A Comparative Analysis of Post-market Surveillance for Natural Health Products (NHPs)

Thesis

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List of Abbreviations

ADR	Adverse Drug Reaction
AR(s)	Adverse Reaction (s)
BfArM	The Federal Institute for Drugs and Medical Devices
CIOMS	Council for International Organizations of Medical Sciences
EC	European Commission
EMA	European Medical Agency
EU	European
FDA	Food and Drug Administration
HCP	Health Care Professionals
ICH	International Conference on Harmonization
MAH	Manufacturing Authorisation Holders
MedDRA	The Medical Dictionary for Regulatory Activities
MEDSAFE	The Medicines and Medical Devices Safety Authority
MHRA	Medicines and Healthcare products Regulatory Agency
NHPs	Natural Health Products
NZ	New Zealand
PCC(s)	Poison Control Centre(s)
PRR	Proportional Reporting Ratio
PSUR(s)	Periodic safety update Report(s)
RMP(s)	Risk management Plan(s)
TGA	Therapeutic Goods Administration
UK	United Kingdom
UMC	Uppsala Monitoring Centre
US	United States
WHO	World Health Organisation
WHO-DD	WHO Drug Dictionary

Abstract

Natural health products (NHPs) are attractive due to the public's perception that they are natural and safe but there is wide variety of risks associated with these products. Post-market surveillance is the key to control hazards produced from NHPs. A set of activities are involved in post-market surveillance designed to assure the safety, efficacy and quality of products after being launched into the market. Although post-market surveillance is an efficient tool to preserve the safety of users from adverse reactions of NHPs but there are various challenges associated with performing post-market surveillance specifically for NHPs. This research project is focused on defining a framework for performing post-market surveillance for NHPs and on identifying best practices in its application. An international comparative analysis was undertaken to formulate best practices by reviewing existing frameworks for post-market surveillance of NHPs in Australia, Germany, New Zealand, United Kingdom and United States. Evidence-based best practices are compared with the Canadian post-market surveillance framework to identify key gaps in the Canadian system. Recommendations are provided for bridging each gap, and making the Canadian NHPs surveillance system, strong according to the international standards of best practices.

Chapter 1: Introduction

The introduction chapter contains four sections, the first background section provides the definition of natural health products (NHPs), size of Canadian market for NHPs, the risks behind usage of NHPs and the importance of post-market surveillance system. The second section, study rational, explains the intention behind choosing this study. The third section presents the research questions and objectives of the research. The last section of this chapter summarizes the structure of the thesis.

1.1 Background

Natural Health Products (NHPs) are naturally occurring substances often referred to as alternative, complimentary, and traditional medicines. According to Health Canada, NHPs include "Chinese medicines, herbal remedies, aurvedic medicines, homeopathic medicines, vitamins minerals, probiotics and other products like amino acids and essential fatty acids" (Health Canada, 2011).

NHPs can be made from plants, micro-organisms and marine sources. Some NHPs have been in use for a long time in many countries of the world. It is reported that "there are approximately 250,000 species of flowering plants on this planet, and 25% to 50% of them have been used at one time or another for medicinal purposes" (Kozyrskyj, 1997, p. 698). NHPs are sold on the market for a variety of health reasons such as promoting and preserving good health, prevention of diseases, and reducing health risks. NHPs are popular because of the perception that they are safe to use and have few side effects as compared to pharmaceuticals.

1.1.1 Size of NHP Market in Canada

The sale and consumption of NHPs are dramatically increasing around the world. It has been found that more than 50% of the American population are using NHPs in a variety of forms. The most prevalent population include women, seniors, people with higher level of income and patients suffering from chronic conditions such as cancer, and rheumatoid arthritis (Kozyrskyj, 1997).

A recent 2010 Natural Health Product Tracking Survey produced by Ipsos Reid for Health Canada showed that 73% of the Canadian population use NHPs on a daily, monthly, or seasonal basis which includes vitamins and minerals, herbal products, and homeopathic medicines (Ipsos, 2011). A similar survey reported people's attitude towards NHPs as follows:

- 85% believe that NHPs are the leading source of health maintenance; and
- 79% of people think NHPs helps in preventing illness and provide strength to their immune system (Ipsos, 2011).

There are approximately 42,000 NHPs available in the Canadian market. These products profess to boost the immune system, improve energy and vascular health, overall health, and well-being (Statistics Canada, 2007). The retail sale of NHPs in 2007 was $1.36 billion as noted in Figure 1 below.

Vitamins and dietary supplements accounted large part of sale, i.e., $ 865 million, followed by herbal/traditional products, slimming and sports nutrition products contributing $246 million, $145 million, and $110 million respectively (Health Canada, 2010). "Canada accounts for about 3% and 10% of the world and the U.S. market on NHPs, respectively" (Bai and ZC Li, 2006, p.2). The following diagram depicts the NHP market size in Canada.

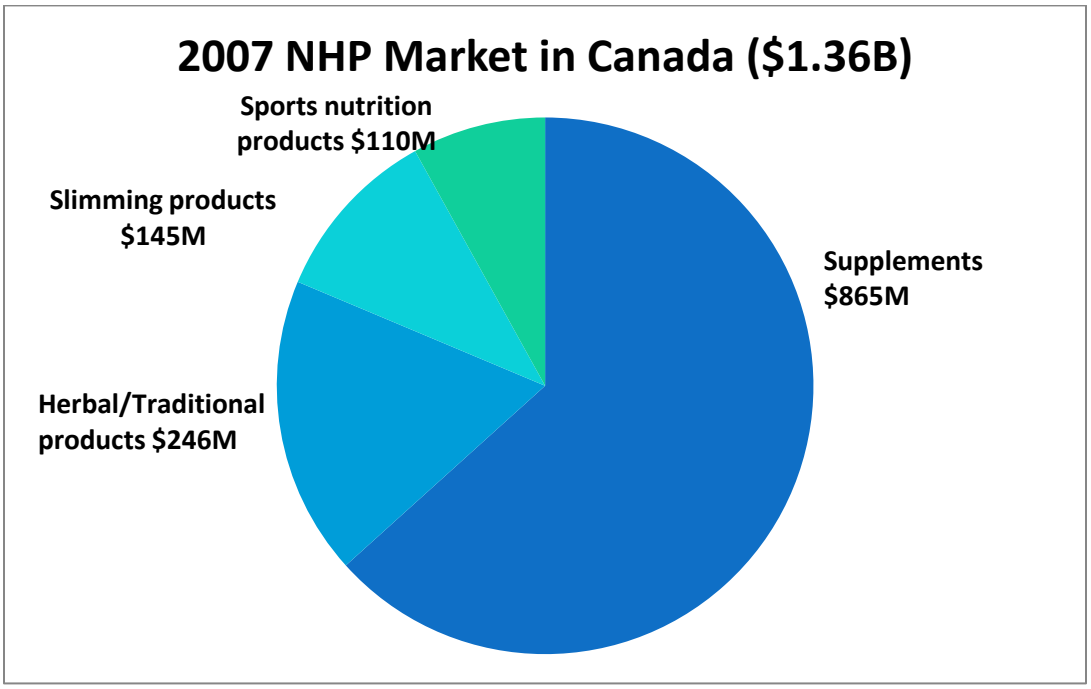

Figure 1.1: The Natural Health Product market size of Canada (Bai and ZC Li, 2006)

1.1.2 Risks in Using NHPs

Although NHPs are considered by the public as safe products because they are made from natural ingredients but they are not risk free. A large proportion of people who are attracted to the use of traditional medicines base this attraction on the false impression that "natural" means safe. With the increased use of NHPs, the incidences of users' experiencing side effects or unwanted reactions have increased significantly over time. A survey by Ipsos reported that, in 2005, 12% of Canadians using NHPs had adverse reactions and in 2010, 15% reported some problems related to these natural products (Ipsos, 2011).

There are a wide variety of risks associated with NHPs which arise due to several reasons such as: contamination of products with metals, unhygienic manufacturing, adulteration with unclaimed medicines,

incorrect dosing and instructions, and unfamiliarity toward the suitability for a specific group (WHO, 2004). These risks are responsible for producing side effects, serious illness or death related adverse events. For example, *Ephedra* is known as a traditional Chinese medicine used for the treatment of asthma, hay fever and the common cold. In 2004, the United States Food and Drug Administration (USFDA) banned the sale of *Ephedra*-containing supplements due to reports of serious side effects and *Ephedra*-related deaths (Jordan et al., 2010). This is one example of numerous NHPs on the market which may pose substantial risk to human life.

1.1.3 Post-market surveillance

Governments are interested in monitoring the quality and safety of marketed products as the key to control potential consumption hazards. Generally, health products are approved based on company-sponsored clinical trials which help to establish potential hazards associated with using given drug. However, it is not a case for most NHPs as most are introduced in the market based on their history of traditional use in the same region or other countries. In such cases, the lack of scientific evidence may imply that threats associated with the general use of NHPs in the marketplace remain unknown. Post-market surveillance is a method designed to detect potential adverse reactions after the public release of the NHP to the market. Post-market surveillance attempts to mitigate risks from emerging adverse reactions toward improving public safety.

The primary aim of post-market surveillance is to monitor the quality, safety, effectiveness and performance of NHPs after they have been introduced in the market (Health Products and Food Branch, 2006). The major activities included in this process are collection of information or reports on adverse reactions, finding a causal relationship between adverse event and product, and, based on the evidence, taking appropriate action. The activities involved in post-market surveillance for NHPs are similar to those for monitoring safety of therapeutic drugs, vaccines or other biological products.

It has been found that post-market surveillance of NHPs is more difficult as compared to pharmaceutical drugs because of the unique challenges associated with these products. As Jordan et al. (2010) note, the major challenges include:

> "Deficiencies in both the quantity of information (e.g. under-reporting of adversereactions, general lack of toxicological information on herbs) and the quality of information (e.g., poor quality of adverse reaction case reports or lack of information on the quality of HMPs associated with case reports submitted to regulatory authorities or published in the scientific literature)." (Jordan et al., 2010, p.199)

Under these conditions, it is hard to identify the causal relationship between NHPs and an adverse reaction. In response, the federal government of Canada gave the responsibility for implementing NHP regulations and post-approval safety surveillance to the Natural Health Product Directorate (NHPD) and Marketed Health Product Directorate (MHPD) of Health Canada. Both directorates are divisions of Health Products and Food Branch of Health Canada. The NHPD regulations are planned to assure that Canadians consume safe and high quality NHPs, while MHPD is responsible for taking a consistent approach to collect adverse event reports, assessment of signals and risk communications related to regulated marketed health products (Marketed Health Products Directorate, 2011).

1.2 Study Rationale

Today, many countries implement a post-market surveillance framework of the NHPs for the safety of their populations. Each country uses their own or similar features to one another for managing NHP adverse reaction risks. The proposed research applies the approach of comparative analysis for recognising best practices for post-market surveillance out of different countries' frameworks. This framework is used to compare to the Canadian surveillance system and propose recommendations to fill gaps between the current and a more effective and desirable post-market surveillance system.

Also, the drug safety, patient care, and post-market monitoring literature have primarily focused on developing new methods or improving single components of post-market surveillance frameworks which are limited to only pilot studies. Fewer studies are available on harmonization of requirements and understanding of complete Post-Market Surveillance (PMS) activities. The proposed research attempts to understand the purpose and connection between the various components of a complete post-market surveillance system, recognise the "best practices" regarding each component, and identify how closely Canadian post-market surveillance components match with these best practices.

1.3 Research questions and objectives

The fundamental research questions proposed in this research are as follows:

1. What are the best practices for NHPs post-market surveillance and how these practices can be framed based on international applications?
2. What is Health Canada's current framework for post-market surveillance of NHPs and how does this compare with the best practices?
3. What are the lessons learned from the comparison of best practices and the Canadian post-market surveillance framework toward developing an improved post-market surveillance system for NHPs in Canada?

In response to these research questions, the research objectives of the proposed work are as follows:

1. Develop a reference framework by summarizing international organisations' guidelines and protocols for post-market surveillance framework to understand the various components of a surveillance system and their functions.
2. Examine the international literature from a variety of sources to discover best practices for NHP Post-Marketing Surveillance; understand the functionality and relationship of the components of a post-market surveillance system, and develop best practices describing the system and its operations.
3. Describe the Canadian NHP post-market surveillance framework, institutional and legal structure, and process flow among stakeholders. Compare and contrast the elements of the existing Canadian NHP post-market surveillance framework with best practices developed from international literature to identify the key gaps
4. Provide recommendations based on best practices for future post-market surveillance of NHPs in the Canadian context.

1.4 Plan of the Research Thesis

This thesis is divided into seven chapters. These are: 1) Introduction; 2) Literature Review; 3) Methodology; 4) Comparative Analysis and Results; 5) Critical Analysis of the Canadian NHP Surveillance System; 6) Recommendations; and 7) Conclusion. The first chapter provides prologue to the topic, some background information regarding NHPs, study rationale, the research questions and objectives, and the plan of the research. The second chapter is devoted to the literature review of previous work on post-market surveillance of NHPs. The third chapter provides the proposed research methodology for comparative analysis, study design, measurement scheme and data collection procedure. The fourth chapter discusses the formulation of the NHP reference framework, comparative analysis of selected countries and identification of best practices. The fifth chapter describes the Canadian NHP surveillance system and explores the gaps with respect to best practices. Recommendations are provided in Chapter 6 to address the identified gaps. The final chapter presents the conclusions of the overall thesis research.

Chapter 2: Literature Review

The review of the literature is divided into six parts. The first section, 2.1 below presents the Canadian market observations of NHPs which provide information on commonly sold natural health products in the Canadian market, consumers' attitudes and prevalence of using NHPs among consumers, and reasons behind using NHPs. The second section, 2.2 presents the adverse reactions caused by NHPs, and gives examples of natural products that produced adverse reactions and were later banned from the Canadian as well as international market. The third section, 2.3 presents post-market surveillance which is further categorised into three sub-sections, i.e., (i) types of post-market surveillance; (ii) challenges associated with monitoring NHPs' adverse reaction; and (iii) international post-market surveillance frameworks of different countries including the USA, Europe, Australia and UK. The fourth section 2.4, gives the review of those international organizations which provide guidelines to perform various post-market surveillance activities. Further, the section 2.5 introduces comparative analysis and provides examples of healthcare research in which comparative analysis was used. The last section, 2.6 summaries the literature review.

2.1 Canadian Market Observation of NHPs

The NHPs gained public attention due to perceived safe use and a fact that they are made from natural ingredients. There are studies that focused on trends of using NHPs in Canada and the attitude of people toward using these products. A report on the use of NHPs in Canada based on Baseline Natural Health Products Survey 2005, showed that 86% of Canadians think that NHPs are a good source of maintaining and promoting health, and supported the right of Canadians' to use NHPs (Reid, 2005). The survey reported that 19% of Canadians consider that "If a health product is made of natural substances, there are no risks associated with its use" (Reid, 2005, p. 13).

A study by Singh and Lavine (2006) assessed the prevalence of NHPs among adults in Canada using the 2000-2001 National Population Health Survey (Statistics Canada, 2000). This survey was conducted by Statistics Canada and 11,424 adults participated in the study. Researchers evaluated the use of NHPs by age, gender, socioeconomic status and disease state. According to the Survey, a significant proportion of the Canadian population uses alternative medicines. Women scored higher in comparison to men (11.5% vs. 7.1%), middle age and older Canadians as compared to young adults (50% higher) and people in poor health reported more frequent use of NHPs. The most frequent products were Glucosamine, Echinacea, Garlic, Vitamins and Minerals. People suffering with certain diseases such as fibromyalgia, inflammatory bowel disease, and urinary incontinence were more prevalent to use NHPs.

The study conducted by Brazier et al. (2001) demonstrated the use of natural health products by Ontario seniors. Researchers conducted a telephone survey in four Ontario communities. There were 1071

respondents to their survey of age 60 or older. This study reported that more than 20% of the respondents self-experimented with NHPs without getting any recommendations from doctors, pharmacist, herbalist or other sources. Among respondents, 38% old age people never disclose their physicians that they are using any kind of herbal products with other therapeutic medicines. The reasons for using alternative medicines were that they were less expensive than pharmaceuticals, and the belief that NHPs were safer than prescription drugs. Another fact this study revealed was that almost half of the respondents (49%) supported the notion that government should pay for herbal medicines along with prescription drugs.

2.2 Monitoring Adverse Reactions from NHPs

Adverse reactions are a harmful response caused by normal use of medication or NHP. According to Health Canada, "adverse reactions are undesirable effects to health products. Reactions may occur under normal use conditions of the product. Reactions may be evident within minutes or years after exposure to the product and may range from minor reactions like a skin rash to serious and life-threatening events such as a heart attack or liver damage" (MedEffect-Health Canada 2009).

The use of NHPs can be associated with adverse reactions that lead to a demand for careful monitoring of these products. There are various studies that looked on adverse reactions produced by different NHPs. For example, Proplis is a bee derivative herbal product that claims to treat diseases such as dermatitis, laryngitis, and oral ulcers because of its antiviral and antifungal properties. A study by Menniti-Ippolito et al. (2008) reported that the Italian government received 18 suspected adverse reaction reports and 16 reports of allergic reactions related to Propolis in the period 2002-2007. Some reactions were serious enough that patients had to visit emergency departments and two of these patients reported a life-threatening event. Researchers revealed that these products were available in the Italian market without any label warnings of possible adverse reactions.

Bensoussan et al. (2000) investigated the nature and frequency of adverse events produced from the traditional Chinese medicine (TCM) in Australia. The study was considered to be extensive because researchers included representatives of all health occupations that practice TCM. They conducted a survey on TCM practitioners or health groups and asked to indicate the frequency of adverse events, they noticed in their customers, from the consumption of Chinese herbal medicines during their practice lifetime. 1100 practitioners responded to the survey and results demonstrated more than 800 adverse events were produced by TCM. Gastrointestinal symptoms were the most common adverse reaction reported by practitioners. Other than that, fainting and dizziness, and significant skin reaction were the next frequent adverse reactions noticed by TCM practitioner. Also, some TCM groups reported serious effects such as central nervous system effects, renal toxicity, and death due to the consumption of these alternative medicines. The study revealed significant information that TCM practitioners noticed in their customers

an average of 1 adverse event every 8 to 9 months of full-time practice or 1 adverse event for every 633 consultations.

With the increase use of NHPs, a rise in adverse reactions has been noticed. In Canada, the adverse reaction reports due to NHPs occurred among 12% of people using NHPs in 2005. This figure rose to 15% in 2010 (Ipsos, 2011). Historically, NHPs have been withdrawn from the Canadian market after receiving adverse reaction reports. These products included: *Piper methysticum* (Kava), *Glucosamine sulphate*, *Ginko biloba*, and products containing *Aristolochia*, *Ephedra* or *Ephedrine* (WHO, 2002). Although some of these products and ingredients are still licensed in Canada in certain circumstances, e.g., *Aristolochia* but can be licensed in extremely dilute homeopathic products. In the period of 1998 to 2005, Health Canada received 7 reports of adverse reactions associated to the consumption of black cohosh, a traditionally used herb remedy used to treat variety of disease but widely used for the treatment of symptom relief during and after the menopause. The symptoms of adverse reaction to this herbal medicine included gastrointestinal irritation, headaches, faintness and queasiness. Also, there were some cases of liver dysfunction expected to associate with the use of black cohosh (Health Canada, 2007).

2.3 Post-market Surveillance

Post-market surveillance is important for monitoring the safety of health products after being released to the market. It is a tool for tracing adverse reactions produced by NHPs, detecting significant causal relationship between a product and disease and informing others regarding product safety (WHO, 2002).

The Canadian Institutes of Health Research defined post-market surveillance as:

> "Post-market surveillance is the continued monitoring for, and the study of effects and other, safety and effectiveness related aspects of, health products that have been marketed to the public." (CIHR, 2008, p. 1)

According to Health Canada, "Post-market surveillance is essential in detecting and addressing safety issues and ensuring that a balance is maintained between the health benefits and the risks posed by all health products" (Health Canada, 2007, p. 1). The chemical composition of NHPs may vary according to the different extraction procedures, preparation methods, contaminations, or adulterations which can pose risk to a diverse population (IRAC, 2002; Rosenbaum, 2002). Also there is lack of information on the impact of NHPs to specific groups of the population such as children, old age people, women, and people suffering with certain medical conditions. As there are few NHPs that undergo clinical trials and come to the market based on their traditional use, the lack of scientific evidence on safe use of NHPs urge the need of performing an efficient post-market surveillance which can assure public safety and trust. Post-market surveillance can be an important tool to detecting different benefits and harms of NHPs when they are

introduced in the market and large numbers of people become exposed to these products (Fuller and Saibil, 2005). The main advantages of post-market surveillance include, "an early warning for removal of suspect product from the market resulting in increased user and patient safety, reduced litigation, providing feedback to research and development (R&D) groups to improve existing products, robust Quality Management System and greater regulatory standards compliance" (Hegde and Konakanchi, 2011, p.2).

2.3.1 Types of Post-market Surveillance

Post-market surveillance requires a careful structured methodological approach. To strengthen the surveillance tool, different approaches are being developed at the regulatory level and the scientific level. The regulatory level consists of conditional approval of health products and submission of risk management plans by manufacturing authorities. The scientific level consists of active involvement of consumers, industries and healthcare professionals (Härmark and Van Groothees, 2008). There are mainly four types of post-market surveillance: passive surveillance, active surveillance, controlled clinical trials and observational studies

Passive Surveillance. Some methods of passive surveillance include spontaneous reporting or volunteer reporting and mandatory reporting. Spontaneous reporting is the most commonly used method for data collection and monitoring of adverse reactions. The article by Härmark and Van Groothees (2008) provided the explanation of spontaneous reporting, its advantages and disadvantages. The main objective of spontaneous reporting is the early detection of signals of adverse reactions. In this system, physicians, pharmacists, and consumers voluntarily report any suspected reaction due to the use of health product. The main advantage of spontaneous reporting is that its scope is national and able to cover diverse populations. In this passive surveillance, the most severe and unexpected cases are reported which is helpful in detecting signal more rapidly. The major disadvantages of this system include underreporting and poor quality of reports.

Active Surveillance. The active surveillance system can be defined as "regular periodic collection of case reports, of drug events, from health care providers or facilities" (Medeffect-Health Canada, 2008, p.3). The major objectives of active surveillance includes collecting adverse reaction reports by focusing on events, settings, or products of interest, recognise drug safety signal and confirm signals identified through passive surveillance (FDA, 2009). This form of surveillance was developed in New Zealand and UK between 1970 and 1980 (Härmark and Van Groothees, 2008). Active surveillance system uses more rigorous and/or purpose-designed data collection tools. The methods of conducting active surveillance involves pilot studies in specific settings, non-interventional observational cohort studies, real-time queries/surveys or targeted studies of important potential health product problems, electronic Surveillance

System, direct observations, etc. One of the key benefits of active surveillance includes intensive monitoring in natural settings and ongoing assessment. Also, it has been considered that active surveillance is a key to improve the quantity of adverse reaction reports. Jordan, Cunningham and Marles (2009) provided an example of active surveillance, in which a pilot study named SONAR (Study Of Natural health products Adverse Reaction) was conducted in Canada to increase the reporting of adverse reactions related to NHPs. This pilot study was focused on noting any adverse reaction caused by drug/herbal interaction and designed to ask questions by pharmacy staff from the patients who visit pharmacies to pick medications. These questions were related to the use of NHPs and prescription drugs at the same time in the past 3 months, and if they felt any side effect or allergic reaction during the use of these natural products. Researchers mentioned that active surveillance programs such as SONAR and educational activities which make the public and health professionals more aware to report adverse reactions, can improve the issue of under-reporting. Other than benefits of active surveillance, there are some disadvantages which include the possibility of selection bias of reporters and patients, and requirement of more intense resources which makes it expensive (Murty, 2007; Härmark and Van Groothees, 2008; Shakir, 2007).

The Controlled Clinical Trials are useful in clarifying the mechanism of adverse reactions, examination of post-market safety issues and recognising the means of prevention (EMA, 2000). These trails involve treatment and controlled groups which are matched as closely as possible. For minimizing the biases, randomizations and double-blinding" techniques are used (United States, 1982). Yeh, Lin and Liu (2007) conducted a randomised, double-blinded, placebo-Controlled trial to access the effectiveness and safety of traditional Chinese herbal product called Four-Agent-Decoction. This specific traditional Chinese product is widely used in Taiwan to relive women menstrual discomfort called Dysmenorrhea. The study was conducted in ad-hoc clinic settings at a teaching hospital in Taipei, Taiwan. Researchers enrolled seventy-eight primary dysmenorrheal young women and randomized the participants into Four-Agents-Decoction or placebo groups based on the order of their chosen date and the arrival time for their post-screening clinic. The two groups called treatment and placebo group were allocated with 39 women each using the computer generated allocation technique. Further, for maintaining the blinding standards, study product and placebo capsules were kept identical. The study revealed that both the overall-pain and peak-pain decreased in the Four-Agents-Decoction (Si Wu Tang) group and increased in the placebo group but the differences between the two groups were not statistically significant. Also, there was no difference in adverse symptoms between the Four-Agents-Decoction and placebo groups.

The controlled clinical trials are regarded the effective method for assessing a drug's efficacy and safety but there are several limitations involved with them. The high cost and non-feasibility of these trials in

certain situations, for example, these studies are conducted relatively for short duration and detect only acute or subacute effects. Clinical trials are impractical when NHPs effects are rare or visible only after long-term use or a long latency period (United States, 1982). Other than that, the methodological limits such as need of several therapists, more complexity and lack of clarification about the mechanism of action (Firenzuoli & Gori, 2007).

"The Observational Studies are less rigorous than clinical trials, but have the potential to provide information from a representative sample of 'real-life' patients and follow a defined group of patients for a long period of time" (Lawson, 1994, p. 65). There are two main commonly used designs for an observational study for post-marketing research: (1) cohort study and (2) a case control study (Zhou & Yang, 2013). In cohort studies, the two groups called treatment and control are studied in parallel from the beginning of drug use. The treatment group taking the drug of interest is followed to see if adverse reaction occurs whereas control group, who are with the same medical condition but not taking the drug, is followed in parallel to identify the occurrence of any condition due to causes other than drug (United States, 1982). In case control studies, patients having ADR of interest and a suitable parallel control group are selected. The researchers compare the use of the study drug in the cases and the controls to find whether the ADR is related with the study drug (Zhou & Yang, 2013).

The researcher Kiri (2012) reported that most of the European Medicines Agency's jurisdictions are involved in conducting observational studies for exploring and collecting evidences on how products perform in the real world. Also, a similar trend is arising in the US to conduct an increased number of observational studies for finding the safety and efficacy of health products. Zhou and Yang (2013) research suggest that although the observational studies are useful in determining a drug's beneficial as well as adverse effects but they are expensive, complex to maintain, and their use still requires careful design and analysis. Also, observational studies are liable to confounding and estimation of the causal effect of a drug versus a comparative one is very challenging.

2.3.2 Challenges for Post-market Surveillance

Many countries face various difficulties in implementing post-market surveillance of NHPs. It has been considered that monitoring safety of NHPs is more challenging in comparison to therapeutic drugs. These challenges are related to causality assessment of adverse reaction, inadequate knowledge regarding characteristics of NHPs, underreporting of adverse reactions and general issues in signal detection.

The important issue in assessing the causality of adverse reaction is to recognise elements that contribute to the poor quality of NHPs. Herbal products are complex in nature and its structural properties can vary

according to manufacturing or extraction technique, cultivation areas and changes in harvest times. These variations can shift the actual target of NHPs. Most of the alternative medicines are mixtures of multiple herbs and ingredients that may cause adverse reactions. In these cases, it is hard to identify the causality to the product as a whole (Siow et al. 2005). The contamination of NHPs due to heavy metals and microbes is one of the major concerns. The reasons for these contaminations are inadequate quality control system or hygiene practices, traditional preparation methods, growth of heavy metals or microbes through environment, use of fertilizer during cultivation, etc. These factors blur the actual impact of NHPs on human body and pose difficulties in detecting whether adverse reaction was due to original product or due to these contaminations (Jordan, Cunningham, and Marles, 2010). The other difficulties in assessing causality are adverse reactions produced from, mistaken use of wrong herbs and drug-herb interactions.

The inadequate knowledge regarding complex characteristics of NHPs, appropriate evaluation methods (safety, efficacy, harms/benefits) and unsuitability to specific population groups pose the greatest challenge to monitoring the safety of NHPs. NHPs have been in use for centuries as traditional medicines, however, only a few scientific research and evidence-based studies have been performed to access the safety and efficacy of these products. There are limited publications or data available that can provide reliable information regarding the risks and benefits of using NHPs. In most countries, the important source of adverse reactions produced by NHPs is spontaneous reporting from consumers and health professionals, and published reports. Usually these published reports are based on single case series which are not very helpful in identifying the true relationship between disease and NHPs (WHO, 2005; Jordan et al., 2010).

The under-reporting of adverse reactions related to NHPs is a major issue in most countries. The main reason of underreporting is due to the fact that most of the consumers consider that NHPs are safe and there could not be any side effect with the use of these products. Generally, patients don't disclose the use of NHPs to their physicians as they think that NHPs are always safe. It makes a physician's ability to treat a patient more challenging if he/she is not familiar with what NHPs the patient is taking. The major drawback of this misconception is that regulatory authorities couldn't obtain sufficient amount of reports to confirm a signal and identifying risks related to a specific NHP (Vohra, MacKenzie, and Clifford, 2005; Shetti, Kumar, Sriwastava and Sharma, 2011).

The *general issues in signal detection* include high background noise, unknown denominator problems and reporting bias. Most of these issues are associated with inherent limitation of spontaneous reporting and these increase challenges in signal detection. Noise is defined as the "information which is not part of a signal or which interferes with or obscures a signal" (WHO, 2007). *The background noise* becomes very high in incidences where the progression of disease such as Carcinoma is natural phenomena due to age or

background history of a patient. In these cases, increase in mortality rate is associated with medical or herbal product is difficult to detect (Arora, 2012). The other factors of high background noise are poor quality of AR reports, inappropriate coding for developing case series and insufficient data on drug usage (Arora, 2012; WHO, 2007).

The lack or absence of denominator poses difficulties in interpretation of the data in generating safety signals and putting signals into context (Alghabban, 2004). For putting the newly identified risk into perspective, it is important to quantify it in terms of incidence (CIOMS, 1998). The possible denominators are number of individuals/ patients who are/were exposed to the health product, number of patients exposed to the duration of drug and number of unique individuals dispensed the drug (CIOMS, 2010). Due to insufficient details and underreporting in spontaneous reporting system, it is very difficult to identify the denominator (Arora, 2012). The Pfizer (2011) provided an example of denominator problem when generating a safety signal. According to them, "if 20 individual safety reports report a specific adverse event when taking drug A, this is unclear that whether this represents 20 out of 250 comparable patients using the drug in the real world, or 20 out of 10,000. And if 80 individual safety reports of that same adverse event are reported for drug B (again, without knowing the relevant denominator for both drugs), how does this compare to drug A" (Pfizer, 2011, p.1). It makes interpretation of the data difficult.

Reporting Bias can be defined as selective revealing or suppression of information that leads to an error in the estimating the effects of an exposure on risk. The reporting biases significantly contribute in false positive (over-reporting) and false negatives (over-reporting). An example of bias reporting, called as notoriety bias, is increased number of reports after publication of a news letter indicating association of a health product with a novel adverse reaction, issuance of a safety alerts or drug withdrawal. Thus, after publication, there are more spontaneous reports (Moore et al 2003; Arora, 2012; van Puijenbroek, van Grootheest, Diemont, Leufkens, Egberts, 2001). Another type of reporting bias take place when health care professionals do not report labeled ARs by assuming that known and expected ARs not required reporting. This bias pose many difficulties in finding other aspects than known such as drug-drug interaction, frequency of AR higher that earlier estimations, subgroup of population at low or high risk (Arora, 2012).

2.3.3 International Post-market Surveillance Frameworks

The regulatory and post-market surveillance system differs between countries. The following presents the summary of different countries' post-market surveillance frameworks.

United States of America. In the United States, the FDA (Food and Drug Administration) is responsible for conducting post-market surveillance. According to the Dietary Supplement Health and Education Act

of 1994, natural health products are regulated as dietary supplements, a subset of foods (Jordan, Cunningham, and Marles, 2010). The FDA implemented a passive surveillance system in which it collected adverse effect reports from manufacturers, health professionals and consumers. Manufacturers are liable to submit adverse effects reports but health professionals and consumers report on a volunteer basis through MedWatch online reporting, by phone, email or post (Dart, 2009). The data contained in MedWatch are entered into a computerized database called Adverse Event Reporting System (AERS) which is further evaluated by multidisciplinary experts for causal assessment. If the relationship between disease and drug is confirmed, the information is distributed among stakeholders such as healthcare professionals, consumers and other regulatory agencies. FDA's post-market responsibilities include monitoring volunteer reporting and product safety information such as labelling, company claims, etc., (FDA, 2009).

Australia. In Australia, the Therapeutic Goods Administration (TGA) is responsible for regulating and conducting post-market surveillance of NHPs. These products are listed as low risk medicines in the Australian Register of Therapeutic Goods (ARTG) based on manufacturer's information on toxicity, dosage information, drug interaction/side effects and adverse reactions. According to the Therapeutic Goods Act 1989, the TGA has the authority to cancel immediately a listed product if the application is falsely certified or the product doesn't qualify all listing requirements (Boyd, 2002). In January 2010, an Advisory Committee on Complementary Medicines (ACCM) was established to advise and to make recommendations on complementary medicines to the TGA (Therapeutic Goods Administration, 2011a). The NHP manufacturing companies are required to submit a risk management plan which includes post-market risk management strategies. Sponsors or manufacturers are obliged to submit regular post-market reports and inform the TGA regarding any international safety concerns that emerge related to their product. The TGA responsibilities include conducting notified or un-notified audit of Good Manufacturing Practices (GMP), collecting adverse reaction reports, gathering random and/or targeted samples for laboratory testing, controlling advertisements, etc. In Australia, passive surveillance system is used in which adverse reaction reports are collected through the 'blue card' scheme (an AR reporting form periodically distributed to health professionals), online reporting, phone, email and adverse reaction forum by post. An expert committee assesses the adverse reaction reports and identifies the signal. Once a problem is identified, a number of actions are taken to inform and communicate risks (Jordan, et al., 2010; Wiktorowicz, et al., 2011; Hammett and Hunt, 2009).

Germany. The Federal Institute for Drugs and Medical Devices (BfArM) is responsible for conducting post-market surveillance activities related to NHPs. These products are sold in German pharmacies by prescription and the same regulations apply as for therapeutic drugs. The BfArM is the central office for

receiving adverse reactions reports from regional centres and it collaborates with the WHO international centre for drug safety (Swissmedic, 2009). The NHP market authorities get approval for selling product in Germany based on specific quality, safety, and efficacy requirements. The GMP rules used for pharmaceuticals are applicable to NHPs and legally, market authorizations have to submit monographs containing information on ingredients, doses, formulations, and labelling (WHO, 2005). A passive and active surveillance system is used to collect adverse drug reaction reports. The patients or consumer can download a yellow reporting form from the BfArm website or they can order through mail from regional centres. These reports are further evaluated by regional centres and forwarded to national centre for pharmacovigilance. In case of finding a causal relationship between a product and adverse reaction, risk is communicated through various channels and a number of actions are taken to manage those risks ((BfArM, 2009; WHO, 2005).

European Union. In Europe, the European Medicines Agency (EMA) is responsible for conducting post-market surveillance. If alternative medicines claim to treat illness or physiological functions, they come under regular medicinal products and the same drug regulations are applied to them. EMA approves a health product based on proof of quality, safety, and efficacy (European Medicines Agency, 2012). When a product has known safety issues, manufacturers are liable to submit a risk management plan that describes how safety concerns will be recognized and alleviated after introducing a product to the market. If there is any chance of limited information on products, specific follow-ups measures are required to be undertaken by manufacturing companies (Gough, 2005). To verify that a company is manufacturing product according to European regulations, the EMA can carry announced or unannounced inspection in the industry. "A committee on Herbal Medicinal Products (HMPC) at the European Medicines Agency is established to assist the harmonization of procedures and provisions concerning herbal medicinal products laid down in EU Member States and to further integrate herbal medicinal products in the European regulatory framework" (Routledge, 2008, p.417). The EMA monitors the safety of NHPs largely through passive surveillance. It collects adverse effects reports using a spontaneous reporting system. EudraVigilance is an online system used for reporting and evaluating suspected cases of adverse reactions to a health product. The data stored in EudraVigilance are analysed every month and are used for detecting signals by the multidisciplinary advisory group (Calapai, 2008; EMA, 2012; Mann and Andrew, 2007).

United Kingdom. In the United Kingdom, the Medicine and Healthcare Products Regulatory Agency (MHRA) is responsible for post-market surveillance of NHPs. Product manufacturing companies are required to satisfy the quality, safety, and efficacy of their product to MHRA (MHRA, 2011a). Herbal products are categorised as licensed and unlicensed products. In the case of licensed products,

manufacturers have the legal obligation to pass on reports to MHRA if they receive any adverse reaction report related to their product. However, there is no compulsion for unlicensed herbal product manufacturers to do the same (Gough, 2005). In the UK, the yellow card scheme is the main method of collecting adverse reaction reports from health professionals and consumers (McLernon et al., 2010). The Yellow Card is a spontaneous reporting method or passive surveillance method administered by MHRA with the support of five Yellow Card Centres (MHRA, 2011a). The other reporting mediums are electronic reporting on the Internet, and direct telephone calling by consumers. All reports are saved in the ADROIT (Adverse Drug Reaction On-Line Information) database, which is further used to detect signals. The next steps include assessing risk and benefits, and communicating those risks to different stakeholders. An advisory group made up of experts of different backgrounds is established to advise MHRA on the issues related to NHPs (Barnes, 2003; Mann and Andrew, 2007).

2.4 International Organisations

There are number of international organisations involved in the promotion of technical and scientific aspects of drug and herbal medicines safety. These international organisations/groups publish guidelines, protocols and recommendations for the efficient implementation of various components of post-market surveillance system and taken up new initiatives to guide manufacturers and regulatory agencies. These groups include: (i) The Council for International Organizations of Medical Sciences (CIOMS); (ii) The International Conference on Harmonisation (ICH); and (iii) The World Health Organisation (WHO).

CIOMS. CIOMS was established in 1949 by the WHO and UNESCO as a non-governmental and non-profit organisation. For almost two decades, CIOMS is working as a useful forum and platform for regulators to discuss the various key topics of post-market surveillance (Tsintis & La Mache, 2004). There are various working groups formulated in CIOMS to discuss and develop appropriate and useful guidance for companies, regulatory authorities and academic sponsors in the field of biomedical sciences, pharmacovigilance, drug development, etc. These working groups are comprised of worldwide senior scientists from drug regulatory authorities and pharmaceutical companies. The senior scientists are chosen on the basis of their areas of expertise. Also, CIOMS plays an important role in maintaining the collaborative relations with the United Nations and its specialized agencies such as WHO, UNESCO (CIOMS, 2013; Tsintis & La Mache, 2004). The publications such as "Current Challenges in Pharmacovigilance: Pragmatic Approaches" and "Practical aspects of signal detection in pharmacovigilance" are the important contributions of CIOMS in drug safety and development (CIOMS, 2013).

ICH. The ICH was established in 1990 and making continuous efforts to bring regulators, industry and other experts together to harmonise technical requirements for the various aspects of post-market

surveillance. The countries US, European Union and Japan are the active members of ICH whereas Canada is official observer to the (ICH) and committed to the adoption and implementation of ICH guidance and standards (Health Canada, February 15, 2011). The objective of ICH is to ease the need to duplicate testing carried out during the research and expansion of new medicines by suggesting conducts to attain greater harmonisation in the understanding and application of technical guidelines and requirements for product registration (ICH, 2013 March). The guidelines produced by ICH gives a high level of direction on good practices in the design and conduct of post-authorization studies (Tsintis & La Mache, 2004). ICH has provided over 50 guidelines on technical requirements on quality, safety and efficacy of medicinal products. The important contributions of ICH includes the development of electronic Standards for the transfer of regulatory information and Medical dictionary for adverse event reporting and coding of clinical trial data (MedDRA) (ICH, 2013). The reports called "ICH Harmonised Tripartite Guideline Pharmacovigilance Planning E2E" and "ICH Harmonised Tripartite Guideline Post-Approval Safety Data Management" provides guidance on the available methodologies in conducting good pharmacovigilance practices and good case management practices (ICH, 2003 & 2004).

WHO. The World Health Organisation (WHO) is the directing and managing power for health within the United Nations system. "It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends" (WHO, 2013). WHO published the various technical guidelines to assist countries in the development of policies, regulations and monitoring practices of herbal medicines/NHPs with the increase of NHPs consumption among consumers and adverse event reports, (Ajazuddin & Saraf, 2012). These guidelines recognized the importance of herbal medicines to the health of many people throughout the world and assist Member States to strengthen national capacity in monitoring the safety of herbal medicines (Ajazuddin & Saraf, 2012; WHO, 2004). The various reports, such as WHO guidelines on the safety monitoring of herbal medicines in pharmacovigilance system, Good agricultural and collection practices for medicinal plants, National policy on TM and regulations of medicines, etc., are the few of WHO's contributions in providing guidance to the regulatory authorities, manufacturers and research units on the available methods and practices for an efficient NHPs post-market surveillance system (WHO, 2003; WHO 2004).

2.5 Comparative Analysis

Comparative analysis is an instrument to recognise and verify the variations between multiple systems, to investigate why these variations took place and to draw policy lessons. It is central to understanding the nature of the gap between multiple systems and the efforts to bridge this gap. The comparative analysis reveals not only diversity in systems, but the striking unevenness in the quality and standards of

implementing these systems in practice (Wiktorowicz et al 2012). It addresses how a given system compares with others in a number of key areas, helps in learning the strengths of other system and draws some themes for considerations in assessing strategic directions of a given system in future (Government of Canada Translation Bureau, 2012). According to Marchildon (2005), comparative analysis is an optimized tool for identifying similar issues/problems, and relating experiences gained by other countries to our own national situations.

2.5.1 Comparative analysis in Health Care studies

Various researchers used comparative analysis on a wide variety of areas such as health, social, culture, education and diverse public services. The following paragraphs present such examples related to healthcare.

Marchildon (2005) compared the Canadian health care system with the systems in Australia, France, Sweden, the United Kingdom and the United States. These countries were selected based on similarities in size, wealth and government structure, and high quality in health care services. This comprehensive study demonstrated the comparisons among different countries on various aspects of health care industry such as mortality rate, financial resources, organizational structures, health care expenditure, overall health status, health care technologies, health care policies, etc., and judged the performance of Canada. In the end, Marchildon highlighted the areas and challenges in the Canadian healthcare system that need to addressed in the future.

Another example of comparative analysis is a study by Smith (1999) that compared the strategies and approaches used for delivering primary care services to racial/ethnic minority population in the United States and United Kingdom. Through this research, the impacts of social, political, cultural and economic structure of each country on development of primary health care are analysed. The goal of the study was not to identify those factors that were common in both countries, but to recognize those elements which were unique or specific to the primary care for minority groups in each country. Through this comparison, researchers were able to provide results in terms of what works, what doesn't work, best practices, and lessons learned from each system. Based on comparative analysis, recommendations were provided for delivering effective primary care services to the population and collaboration of planning processes or studies of both countries.

A recent study by Wiktorowicz et al. (2012) compared the therapeutic post-market active surveillance approaches used by European Union (EU), United Kingdom (UK), France, US and Canada. The main objective of this research was to conduct a comparative analysis on government's regulatory and decision making process, funding for post-market studies, research standards and legal authorities to public for

accessing data. Semi-structured key informative interviews and document review methods were used to gather information on government's strategies applied for active surveillance. Researchers formulated criteria for comparison and described each countries relevant characteristic under the heading of specified criteria. The difference in policies, funding systems and legal obligations for public were demonstrated through tables and provided recommendations for improving the gaps in Canadian existing system.

2.5.2 Method of Comparative Analysis

For applying a comparative analysis in a study, there is need to consider some important aspects. The selection of cases is the most important aspect for applying comparative analysis in a study. The underlying assumption of a comparative study is to choose cases which fit to a general pattern of the study. They should be similar in some respects but differ in other aspects so that their features can be comparable (Routio, 2007). The comparators are referred as cases or an object of study. Each case could have several observations and differences between cases reveal the underlying structure for variations. Another important part of comparative study is to decide the interesting features, characteristics or attributes that researcher wants to note and compare for the each case. These key features for comparison are referred to as variables or criteria which help to explore variation in cross-national, cross-cultural, cross-issues and cross-institute comparisons. For comparison purposes, an individual case is described as raw material and used to examine the differences/similarities in characteristics of selected cases. The comparison can be depicted in the form of tables, summaries or defining relevant characterises of each case below formulated categories. The results of comparative analyses are useful to highlight the areas of differences within the cases that need future implications (Lor, 2011).

Like other research methods, comparative analysis is not limitation free. The major drawback is that the research findings of comparative analysis cannot develop broad generalizations to other processes, systems or countries which were not studied or the part of comparative analysis (Lor, 2011). Specially, if a study consists of only two cases for comparison then it is unwise to claim any result about a wider group (Outhwaite & Turner, 2007).

2.6 Summary of the literature

In summary, this review of the literature has revealed that three in four Canadians use natural health products and a third uses them every day (Ipsos, 2011). The prevalence of NHPs among consumers is high because of the perception that these are safe products. The most prevalent users of NHPs are women, middle age and senior citizens and people suffering from certain medical conditions. NHPs, as with any health product, may produce adverse reactions, or may interact with prescription medicines, depending on inherent toxicity or on how they are used. Post-market surveillance is a key to monitoring the safety of products after being introduced in the market. Active and passive surveillance are the two main

approaches used for managing risks associated with NHPs. There are various challenges involved in performing post-market surveillance of NHPs such as under-reporting, lack of scientific evidences regarding characteristics of these products and detecting signal due to complex nature of herbal products, inadequate processing techniques etc. Various countries have indulged in strengthening their post-market surveillance frameworks. These frameworks are similar in some aspects but different in various features. A comparative analysis approach is useful for analysing the similarities and differences between multiple systems and bridges the gap between variations. The international organisation like CIOMS, ICH and WHO involve in the promotion of technical and scientific aspects of drug and herbal medicines safety by publishing guidelines, protocols and recommendations for regulators, industry and other experts.

The existence of various challenges in performing NHPs post-market surveillance activities, the variation in post-market surveillance framework and the study of international organisations provides an understanding and basis for the foundation of high level standard for countries to perform NHPs post-market surveillance activities. Also, the comparative analysis provides a practical means of determining best practices relative to the high standard, and that the comparative an excellent basis for evaluating the performance of the Canadian system. The Literature Review motivates the proposed research methodology to be presented in Chapter 3 to follow.

Chapter 3: Methodology

This chapter explains the study design, methods, and research process which provide detail of the different steps involved in performing this research. It describes each phase of study with their objectives, inputs, processes and outcomes.

3.1 Study Design

This section describes the logical sequence of performing this research presented in four phases. This section explains each phase of the study with its purpose, procedure and outcomes as follows.

Phase 1: *Development of the reference framework for NHPs post-market surveillance*. The first phase describes the development and structural procedure of developing the reference framework for NHPs post-market surveillance by reviewing the guidelines published by international organisations.

Phase 2: *International Comparative Analysis*. The second phase involves performing a comparative analysis between the developed reference framework of Phase 1, and the NHPs post-market surveillance frameworks in place in Australia, United Kingdom (UK), the United States (US), Germany and New Zealand.

Phase 3: *Identification of International Best Practices*. The third phase results in identifying the best practices for performing NHP post-market surveillance from the international contexts.

Phase 4: *The description of Canadian Surveillance System and Comparison with Best Practices*. The fourth phase presents an overview of the Canadian post-market surveillance framework and performs a comparison between Canadian and NHPs surveillance best practices. Phase four demonstrates the characteristics of different elements of NHP post-market surveillance, the connection between those elements, and the role of different stakeholders in the Canadian context. The results of the fourth phase help to understand how closely the Canadian system matches with the best practices for NHPs post-market surveillance system. Following are the detailed description of each phase of the research process.

Phase 1: Development of a Reference Framework for NHPs Post-market Surveillance System

A review and scoping of published reports, guidelines, manuals and websites produced by the international organisations WHO, ICH, CIOMS resulted in the development of a reference framework for the NHPs Post-market Surveillance System. (See also Appendix A – "Reference Framework Formulation Guidelines", Table –A.1). The reference framework is defined as a set of activities, elements, functions and roles required to operate an efficient post-market surveillance system for NHPs guided by the referenced documents. Such a framework was required to perform a comparative analysis of each selected

nation's post-market surveillance system against a standard surveillance system "reference framework" and to identify each country's system strengths, weaknesses, and gaps to formulate best practices. The following paragraphs describe the system elements developed to formulate the reference framework, namely: (1) Dimensions; (2) Attributes; and (3) Indicators. (The full detail of the developed itemized reference framework is given in Appendix B – "NHP Post-market surveillance Reference Framework")

(1) Dimensions: This term refers to the major components or pillars of the NHPs post-market surveillance system. The six dimensions were constructed by consolidating the common components of the NHP surveillance system that were highlighted by the key reference documents. The six dimensions of the NHP surveillance system are as follows:

1. NHPs Post-market Surveillance System Structure and Stakeholder Coordination: The dimension refers to the different entities which perform together to attain the specific organizational goals. The coordination and collaborations is important to enable the different stakeholders (experts, advisory committees and international organisations) work together, share specialized skills and ensures the harmonious functions of an organisation (Young, 2012)
2. Laws and Regulations for NHPs: This dimension specifies the importance of establishing legal conditions under which NHPs should be organized in accordance with national policies and enforce regulations which are vital for ensuring the safety, quality and efficacy of herbal medicines (WHO, 2005).
3. Sources of NHPs Adverse Reaction Information: The dimension refers to the variety of ARs information sources which contribute the understanding and finding a causal relationship between drug and disease. Competent authorities and marketing authorisation holders should expand their sources for increasing the ability to detect rare adverse reactions associated with NHPs (SPS, 2009).
4. Reporting of Adverse Drug Reactions: The countries are required to implement technologies, standards and tools that facilitate consumers and healthcare professionals to report their complaints regarding any marketed health products (Harrison, 2008).
5. Data Management and Assessment of Case Reports: It refers to the requirements for defined procedures to manage adverse reaction data collected from different sources and technical expertise to assess the case reports for the purpose of finding a relationship between drug and disease (ICH, 2003)
6. Risk Minimization and Communication: This dimension indicates the importance of mitigating risk through accurate and timely communication to different stakeholders,

organized arrangement of quality assurance and taking appropriate actions after identifying a risk

These identified dimensions underlie the structure of post-market surveillance system. These dimensions are easily recognisable in each of the guidelines published by international organisations. The following table, Table 3.1 represents the process of formulating dimensions by taking an example of one dimension, i.e., "Data Management and Assessment of Case Reports" (Dimension 5).

As shown in the Table 3.1, the referenced documents of the organisations WHO, ICH , EMA and Management Science for Health commonly considered "Data Management and Assessment of Case Reports" as an important phase or area of a pharmacovigilance system and provided guidance for its proper implementation in a country. These documents were reviewed to understand the concept, importance and role of this specific dimension in a post-market surveillance framework.

International Organisation	**Guidelines used for the dimension "Data Management and Assessment of Case Reports"**
World Health Organisation (WHO)	**Guideline Document**: WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance system (WHO, 2004) **Description**: This document provides the technical guidance on the major functional areas of a pharmacovigilance system for herbal medicines in existing national drug safety monitoring systems. **Information used to make this specific dimension:** Section 4.4 and 4.5 described Data Management and Assessment of Case Reports as the "major functional area" of a pharmacovigilance system. These sections provided detail on various requirements and methods of handling and assessment of reports on adverse reactions to herbal medicines. This report provided the background information and conceptualizing the specific dimension for herbal medicines or NHPs
The International Conference on Harmonisation (ICH)	**Guideline Document**: ICH Harmonised Tripartite Guideline Post-Approval Safety Data Management: Definitions And Standards For Expedited Reporting E2D (ICH, 2003) **Description:** This document delivers guidelines on definitions and standards for expedited reporting after releasing product in the market, as well as terms and definitions for good case management practices that can be applied in the post-approval phase of the product life cycle **Information used to make this specific dimension:** This report highlights managing collected adverse reaction information, and assessing and identifying adverse reaction as the important phase of post-approval product life cycle. Section 5 gives detailed information on "Good Case Management Practices" and helped to gain knowledge on data privacy laws regarding reporters, importance of finding duplicate reports and role of regulatory authorities. These guidelines helped to understand the importance of

	technical skills, sufficient information and proper documentation procedures for managing and assessing collected data in a functional framework of post-market surveillance system.
European Medicines Agency (EMA)	**Guideline Document:** European Medicine Agency, Guideline on good pharmacovigilance practices: Module VI – Management and reporting of adverse reactions to medicinal products (EMA, 2012) **Description**: This module provides guidelines to marketing authorisation holders (MAH) and regulatory agencies to deal with collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the European Union (EU). **Information used to make this specific dimension:** This report describes the Data Management and Case Assessment as the "key area" of a pharmacovigilance system and provides in-detail guidelines to manufacturers and regulatory authorities to operate and solve various challenges in this area. This reports helped to understand the various requirements and roles of regulatory authorities and manufacturers for managing data and assessing the case reports.
Management Science for health, United States	**Guideline Document:** Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries (SPC, 2009) **Description:** This report provides a comprehensive description and analysis of national pharmacovigilance systems in developing countries by using an indicator-based performance monitoring tool for assessing pharmacovigilance and medicne safety systems. This document informs development and implementation of a improved pharmacovigilance model. **Information used to make this specific dimension:** The given document states that Data Management and Assessment of adverse reaction reports as one of the "major components" of a pharmacovigilance system. This report provides knowledge on requirement of implementing various elements to perform this specific dimension efficiently in a county.

Table 3.1: Dimension Development Process

Similarly, the other major components of NHPs post-market surveillance system were identified as "key areas", "major components", and "highlighted" elements. These are referred to as "dimensions" in the reference framework. Appendix B – "NHP Post-market Surveillance Reference Framework" provides the full presentation of dimension by dimension rationale as in Table 3.1 above.

(2) *Attributes*: This term defines the functional components of each dimension. Attributes represent the distinct functional area and simplify the broad range of a dimension. Also, attributes play an important role as the means to group indicators according to each function of a dimension, and they provide a structural visualization of the reference framework. For example, the dimension

"Data Management and Assessment of Case Reports" refers to the requirements for defined procedures to manage adverse reaction data collected from different sources and technical expertise to assess the case reports for the purpose of finding a relationship between drug and disease. Thus, to separate the two functional elements of the dimension, two attributes were formulated, as follows:

(3) Data Management and Assessment of Case Reports (Dimension 5) Attributes:

Attribute 1: Data Management

Attribute 2: Assessment of Case Reports.

This approach offered the flexibility to take a granular look at each functional area of a dimension and to specify requirements for the optimal implementation of each attribute in a country. Appendix B – "NHP Post-market Surveillance Reference Framework" provides the full presentation of the reference framework attributes by dimension.

(3) Indicators: The indicators are defined as the set of requirements or operating procedures to perform or implement an attribute of the system successfully. In other words, for determining the full or partial implementation of an attribute in the reference framework for a country, measurable items are required and these items are called "indicators". These indicators serve as actual units for comparative analysis between selected nations and the reference framework. Table 3.2 below presents the process of developing and assigning indicators to the corresponding attributes by taking an example of the dimension "Data Management and Assessment of Case Reports". Appendix B – "NHP Post-market Surveillance Reference Framework" provides the full presentation of the reference framework including indicators for each attribute by dimension.

The following describes the steps of applying the indicator development process:

1. Identify the list of recommendations, guidelines, procedures or performance measures to perform or implement each attribute of the dimension "Data Management and Assessment of Case Reports" from the referenced documents published by WHO, ICH and EMA. Examine the list in separate columns under their source document name.
2. Remove and consolidate the identical, repeated, or similar guidelines, procedures or performance measures.

3. Compile the list of all recommendations, guidelines or performance measures under the corresponding attribute of the dimension “Data Management and Assessment of Case Reports” and called them as attribute indicators.

International Organisation	Dimension "Data Management and Assessment of Case Reports"
World Health Organisation (WHO)	**Guideline Document**: WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance system **Guidelines for the Data Management** • For facilitating international comparisons of results and international transfer of data, internationally recognised terminologies and classifications of drugs (ATC, INN) and adverse reactions (e.g. WHOART, MedDRA) should be used • The efforts should be made to make sure proper quality controls standards are implemented on data processing and data elements such as completeness, accuracy and integrity of AR reports. • A system should be established to check for duplications of AR reports. • For facilitating easy access and use of data, computer databases should be managed according to the high a standard • For a non-punitive culture, there should be policies or legislations on maintenance the privacy or confidentiality of patients, healthcare providers and institutes information as well as identity **Guidelines for the Assessment of Case Reports** • The WHO causality categories should be used to assess the case reports. These categories are extensively used and have the advantage of being internationally recognised. • For recognising the efforts of reporters and encouraging them to report in future, the acknowledgment through receipt of each report and required feedback should be given. • The data mining techniques are beneficial for signal detection of previously unrecognized adverse reactions. • Each national pharmacovigilance centre should have a multidisciplinary advisory committee to provide tile feedback, suggestions and discussions on current drug safety issues.
The International Conference on Harmonisation (ICH)	**Guideline Document**: ICH Harmonised Tripartite Guideline Post-Approval Safety Data Management: Definitions And Standards For Expedited Reporting E2D **Recommendation for performing Good Case Management Practices** • The Medical Dictionary for Regulatory Activities (MedDRA) should be used for coding drug and medical information. • For avoiding case duplication, fraud and facilitating follow-ups of patients, it is important to avoid case duplication • There should be privacy laws or legislations on keeping reporters personal information and identity confidential • It is recommended that the recipient carefully check the quality and completeness of the medical information in AR reports regardless of the source of an AR report. • Whenever the information is incomplete in AR reports given by reporter, the immediate follow-up actions should be taken for collection the missing information. • The standards for electronic submission of Individual Case Safety Reports (ICSRs) from manufacturers, according to the ICH E2B/M2 guidelines, should be implemented. • The methods such as calculation of the proportional reporting ratio, Bayesian and other techniques are popular for signal detection.

Management Science for health, United States	**Guideline Document:** Strengthening Pharmaceutical Systems (SPS) Program. 2011. Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance **Performance measures for Data management** • Existence of a database to track pharmacovigilance activities • A system to check completeness, integrity and accurateness of reports • The use of standard terminologies and dictionaries for adverse reactions **Performance measures for Case Assessment** • Capability of country doing signal detection and casualty assessment of case reports • Gathering Experts opinion on assessment of case reports

Using the above mentioned reference documents, compiled the list of all recommendations, guidelines and/or performance measures under the corresponding attribute of the dimension "Data Management and Assessment of Case Reports" and called them as indicators. These indicators were formulated to measure the implementation of their attribute in each selected nation.

Reference Framework	**Attribute 1. "Data Management"** **Indicators** : • Coding of NHPs Adverse Reactions using MedDRA or WHOART • Existence of Computerized Database to store and facilitate access to find the important relationship between drug and disease • Availability of technology for exchange of Information between regulatory authorities and manufacturers according to the ICH standards • A Mechanism in place to check integrity, completeness and duplicates of AR reports • A system to conduct Follow-up actions when the information is incomplete • A national legislation on keeping confidentiality and Security of patient's information	**Attribute 2. "Assessment of Case Reports"** **Indicators**: • Use of WHO causality categories for assessing case reports • Use of Signal Detection Techniques such as PRR, Bayesian methods and others • Personalized feedback and acknowledgement to reporters on the reported association between the drug and reported AR • The assessment of reports should be done in cooperation with an expert panel comprising experts in multidisciplinary areas

Table 3.2: Indicator Development Process

Phase 2: Comparative Analysis of International NHPs Surveillance Frameworks

The purpose of this phase is to provide evidence of best practices in NHP post-marketing surveillance by doing a cross-country comparative analysis of the NHPs post-market surveillance. For performing comparative analysis, a three-step approach was used: a. Case selection and Data Collection; b. Scoring Scheme; c. Assignment of Attribute score. The steps involved in performing the international comparative analysis are described in more detail as follows:

a. Case Selection and Data collection

The case selection is an important aspect of the comparative analysis. The United States, Australia, New Zealand and two European Union countries: the United Kingdom and Germany, were selected because these are developed nations with established post-market surveillance frameworks that may be considered comparable to Canada. They offer similarities in basic features of post-market surveillance which allows for generalizability as well as they are sufficiently diverse to cover a spectrum of approaches (Wiktorowicz et al., 2012). These countries are of particular interest because each provides quality public health care and sufficient data are available about each country's surveillance system. In recent times, these countries have expanded their efforts and resources to advance strategies for performing post-market surveillance. In addition, experiences and lessons learned from these countries can be a source of enlightenment for Canada.

Table 3.3 below provides the list of selected countries along with the name of an organization responsible for post-market surveillance.

Country	Post-market surveillance organisation
Australia	Therapeutic Goods Administration (TGA)
Germany	The Federal Institute for Drugs and Medical Devices (BfArM)
New Zealand (NZ)	The Medicines and Medical Devices Safety Authority (Medsafe)
United Kingdom (UK)	Medicines and Healthcare products Regulatory Agency (MHRA)
United States (US)	Food and Drug Administration (FDA)

Table 3.3: Selected Countries and their National Post-market Surveillance Organisations

Information on each country's surveillance system was collected through websites of national regulatory agencies responsible for conducting NHP post-market surveillance. To supplement the data obtained from organisational websites, published articles in the literature and government reports were reviewed and

compiled. From these compilations, an analysis involving how the reference framework relate to each of countries was completed.

b. Scoring Scheme

The post-market surveillance framework for each country was reviewed and a comparative analysis was conducted within each attribute of a dimension across nations. For performing comparative analysis, a scoring scheme was developed to measure each country's surveillance system in quantitative form according to the implementation of reference framework. The scoring scheme consist numerical scores at the level of indicators to measure how given reference framework indicator is used by selected countries. Each reference framework indicator is intended to measure the implementation of an attribute. Therefore, the rating-scale design should consider aspects of both the indicator format and its level of measurement (Doherty, 2011). In the current research, the development of a scoring scheme was required for the two purposes of:

i. Rating countries' responses to the reference framework indicators (Appendix B) based on their degree or extent of utilization (The findings on each country's surveillance system through literature and document review were considered as responses and scored accordingly.)
ii. Selecting a country which attained highest total attribute score to formulate best practices in the dimensions of the reference framework.

c. Other Scoring Methods

There are several existing platforms that use different approaches to score variables. These scoring approaches are examined below.

The most popular scoring scheme is voting. Voting methods are often used when there is need to select a winning candidate based upon voter's choices or preferences. A voting system enforces rules to ensure valid voting, and how votes are counted and aggregated to yield a final result. The current research problem situation is related to the voting methods in a way that the selected five countries act as candidates, and the reference framework indicators act as voters. The best practices were formulated through the winning country obtaining the highest total attribute score. These scores were given to each country depending upon the implementation of each indicator. Thus, these indicators act as voters which rank countries according to their implementation and cause nations to score highest or lowest. These voting methods are categorised based upon the number of candidates. The simple majority rules if there are only two candidates and in the case of scoring three or more candidates, as in this research, Borda count and Condorcet method may apply (Griffin, 2013). The Borda count method is used to order the candidates according to their sums of ranks, which is a simple summing of expressed voter preferences to achieve a social ranking. Generally, the Borda count method assigns zero points to a voter's least

preferred candidate, 1 point for the next candidate, and (n -1) points for the most preferred (where n is the number of alternatives). The Borda ranking is then determined by ordering the Borda scores (Wu, 2012). Although this method solves the problem of scoring more than two candidates, but it assumes that each voter gives a ranking order to each candidate according to his/her preference (Vaughen, 2012). No individual voter will give the same preference to more than one candidate at the same time. In current research problem, one indicator (voter) is implemented in more than one nation (candidate) at the same level or in similar manner or in other words indicators (voters) give the same preference to more than one country (candidate). Thus, this voting method doesn't solve the present research problem.

A Condorcet method is a voting method that obeys the "Condorcet property" (Schulze, 2003). According to this property, if there is a candidate that is preferred by the voters over each of the other candidates then that candidate should be the winner. In other words, if there is a candidate X that defeats every other candidate in a pair-wise comparison, the candidate X must win. Such a candidate is called a Condorcet winner (Fishburn & Brams, 2002). In some cases, this approach yields no winner which is called Condorcet's voting paradox. In this case, the preferences can be cyclic which means that majority wishes can be in conflict with each other (Pinhal, 2007).

d. Related Work

As discussed above, these approaches do not solve the current research problem of scoring international frameworks adequately .Research conducted by the Fraunhofer Institute for Systems and Innovation Research, handled a similar problem of ranking countries according to the utilization of various performance measures (FISIRK, 2006). The main purpose of this research was to analyse, measure, and compare the European central and EU Member States' agencies performance on different aspects of the pharmacovigilance system. The data were collected from the various European member state regulatory agencies and measured using two different rating-scales (Yes/No, and a 5 point-rating scale) against the defined set of performance measures. The outcome of this report was to discuss strengths and weaknesses of the European member state agencies relevant to their pharmacovigilance systems. Other related research on scoring was performed by Wiktorowicz, Lexchin and Moscou (2012) on comparative analysis of various areas of active surveillance such as governance strategies, policies, implementation, resources and approaches. The data were collected from a number of sources for selected countries and findings that measured either in Yes/No or a three-point rating-scale, i.e., low-moderate-high. The outcome of this study was to present the differences between the North America and Europe in the manner of utilization of active surveillance approaches.

Both of these reports addressed a related problem as faced in the current research. A suitable scaling mechanism was derived from these studies which offers the flexibility to score indicators as per their roles, utilization levels, and produces robust scores for determining best practices.

e. Scoring Method used for Current Research

The above studies used the mix of two different rating scales because their main purpose was to compare different countries' post-market surveillance systems according to the different performance indicators at individual levels. They compared countries separately for each performance indicator and depicted their strengths/weakness, whereas the current study was intended to identify the best practices by accumulating each selected countries' attribute scores. Thus, a uniform single three-point rating-scale (2= already exist, 1= in development, 0= not exist) was introduced in this research to score countries' responses to the reference framework indicators based on their degree of utilization. The scores assigned to each indicator were based upon its definition, what it is intended to measure and what information was available on a specific indicator through documents and literature review **(**FISIRK, 2006**)**. For example, an indicator "The National Research Institute for NHPs" is the important element of NHPs post-market surveillance system structure. The development or implementation of such institute in a country determines the compliance of nation with NHPs post-market surveillance system structure requirements. This compliance can be at varying stages in a county, e.g., the national research institute could be already developed or it could be in its development stage. By considering this, a score was given to this indicator to rank countries, i.e., 2= already exist; 1= in development process; 0= doesn't exist in country.

f. Assignment of Attribute Score

There are sets of attributes in a given dimension and the total score for each country was calculated by taking one attribute at a time. The total score was calculated by adding the values of country's possible responses to the each indicator of an attribute and then moved to the next attribute of the given dimension. The total score for each attribute reached maximum value for a given country was considered as highly scored nation and further utilized in formulating best-practices for NHPs post-market surveillance system. The approach of selecting a highly scored nation as per each attribute helps to produce robust best practices. This approach gives an opportunity to closely screen a specific country which is doing well in a particular attribute but may not in the overall dimension or framework. Also, this approach helps to choose not only the common practices but the unique features of international jurisdiction which lead them to score highest.

Phase 3: Establishment of Best Practices

This phase is focused to identify NHPs post-markets surveillance best practices from the international data from Phase 2 and used for later comparison (in Phase 4) with the Canadian surveillance system to identify the key gaps.

In this step, the best practices were formulated by retrieving the practices followed by the country that attained the highest total attribute score. Here, the highest total attribute score is labelled as best practices score. During formulation of attribute best practices, the following two possible situations were taken into consideration.

Situation 1: A total attribute score reached maximum value for one country; thus the indicators implemented by a given country for a specific attribute are transferred to the best practices framework.

Situation 2: A total attribute score reached maximum and equal value for more than one country; in this case a different approach was used in which two different sets of best practices were formulated called "core" and "supplementary" for each attribute. The "core" practices are the shared indicators whereas "supplementary" practices are the uncommon or unshared indicators used by highest and equal scored countries. In other words, the supplementary practices are unique features implemented by highly scored nations. For a country to satisfy the best practices, all core best practices of an attribute were considered as essential practices and must be followed whereas the implementation of any of the supplementary practices of an attribute adds another layer of sophistication to country's surveillance system.

Phase 4: **Description of Canadian Surveillance System and Comparison with Best Practices**

The objective of this phase was to describe the different components of Canadian NHP post-market surveillance system and to identify the gaps between Canadian and international based best practices for NHPs post-market surveillance. For describing the Canadian surveillance system, information was collected through websites of Health Canada, Natural Health Product Directorate (NHPD) and Marketed Health Product Directorate (MHPD). The documents, reports and articles published by Health Canada which provide information on NHP post-market surveillance were reviewed. To supplement the information, a literature review on Canadian surveillance system for NHPs was conducted using online databases. All information was compiled and organised according to each dimensions and its attributes.

Next, the finding from the Canadian surveillance system was compiled in a comparison table against the reference framework and its score was determined for each attribute using the same scoring scheme defined in Phase 2. Further, an assessment is done to identify the minor and key gaps based on differences

between Canadian and best practices score. These gaps help to identify the areas of concern and requiring further scientific study in the Canada's post-market surveillance system.

The following chapter presents the results of the scored comparative analysis of the international systems and identified evidence based best practices from international comparisons, or results of Phase 2 and Phase 3 of the research process.

Chapter 4: Comparative Analysis and Results

This chapter consists of two sections, i.e., (1) Phase 2: Comparative Analysis of Selected countries' Surveillance system and (2) Phase 3: Identification of Best-Practices. In the first section, a comparative analysis was conducted for the countries: Australia, Germany, New Zealand, United Kingdom and United States against the reference framework. The second section was dedicated to formulate best practices for the each attribute of the reference framework using the scoring scheme described in Chapter 3.

4.1 Comparative Analysis of Selected countries' Surveillance system

In this section, the analysis of the NHPs post-market surveillance system components for selected countries, i.e., Australia, Germany, New Zealand (NZ), United Kingdom (UK) and United States (US) are presented. This analysis compares the county systems with the formulated reference surveillance framework (Appendix B). The comparative analysis was conducted by assigning numeric values to the system indicators of each country according to the implementation of each reference framework indicator. This analysis was performed within each attribute of a dimension and the total attribute score was measured for each international jurisdiction. The detailed definition of each of the six reference framework dimensions along with its attribute and corresponding country indicator values are provided in Appendix B. The Tables C1 to C6 of Appendix C – "The Comparative Analysis of Selected Countries with Reference Framework" gives the summary comparisons of the selected nations. These results are summarized and discussed below by each dimension of the NHP reference framework.

4.1.1 NHPs Post-market Surveillance System Structure and Stakeholder Coordination

This dimension of the NHP reference framework was categorised into two attributes, i.e., Structure Elements, and Coordination and Collaboration of stakeholders. Table 4.1.1 shows the scores given to each country according to the implementation of each indicator. (See also Appendix C.) The following paragraphs discuss the comparative analysis of selected nations.

Attribute 1. Structure Elements: The structural elements of a post-market surveillance system refers to the different entities such as departments, institutes, committees which perform together to attain the specific organizational goals. Table 4.1.1 shows that most countries implemented all the indicators of the given attribute except Germany and New Zealand. These two countries attained lowest score in this specific attribute because they have not established any formal national research institutes specifically for NHPs or herbal medicines, whereas Australia, United Kingdom and United States have multiple research institutes and organisation where NHPs research takes place (WHO, 2005). These research institutes and

organisations conduct their own studies, and provide training and information on NHPs to researchers (MACCAM, 2003; WHO, 2005).

Attribute 2. Coordination and Collaboration of stakeholders: For proper functioning of an organisation, it is important to have coordination and collaboration between the stakeholders such as experts, advisory committees and international organisations. Coordination enables the different stakeholders to work together and ensures the harmonious functions of an organisation whereas collaborations with other organisations are important to share specialized skills, expand knowledge and maximizing the expertise (Young, 2012). As shown in Table 4.1.1, the meetings of expert advisory committees in selected nations were assessed on a rating scale from "very frequent" (5-6 times/ year) to "less frequent" (one one times/year). Australia and United Kingdom were the only two countries whose expert advisory committees meet very frequently to discuss the various safety issues of NHPs and surveillance activities (TGA, 2005; Mann, & Andrews, 2002; MHRA, 2013a). All countries collaborated with WHO's International Drug Monitoring Program and other national monitoring centres to exchange information on adverse events and share interests in promoting public safety (Australian Statistics on Medicines, 2010; Kunac et.al. 2008; BfArM, 2008; Barnes, 2003; FDA, 2012 a). These collaborations help in early recognition of new risks and speedy implementation of safety-relevant measures.

Country	Attribute 1: Structure Elements					Attribute 2: Coordination and collaboration with stakeholders		
	A regulatory agency or relevant department for NHPs	A National Pharmacovigilance Center covering NHPs in their scope	Existence of a Expert Advisory committee on safety of NHPs	Presence of National research Institute for NHPs	Total Attribute Score	Frequent Meetings of advisory committee	Collaboration with WHO and Other National Monitoring Centers	Total Attribute Score
Australia	2	2	2	2	8	2	2	4
Germany	2	2	2	0	6	1	2	3
New Zealand	2	2	2	0	6	1	2	3
United Kingdom	2	2	2	2	8	2	2	4
United States	2	2	2	2	8	1	2	3
Rating Scale	2= Already Exist 1= In development 0= doesn't exist					2=Very Frequent (5-6 times/ year) 1 = Frequent (2-4/year) 0= less frequent (only 1/year)	2= Collaborations with WHO and national monitoring centers 1= Collaborations with only WHO 0= None	
Already Exist: A system, rule , technology or element that has implemented in a country and currently in a functional form **In development**: A system, rule or element that is in the process /development or in plan of implementation and not yet in its functional form **Doesn't Exist:** A system, rule or element that is not implemented nor in the development process								

Table 4.1.1: Scores of Selected Countries for "System Structure and Stakeholder Coordination"

4.1.2 Laws and Regulations for NHPs

In preparing the comparison of laws and regulations for NHPs in selected countries and reference framework, this dimension was categorised into two attributes, i.e., Law and Legislation for NHPs, and Regulations for NHPs manufactures. Following is the brief description of comparative analysis of selected countries for each attribute.

Attribute 1. Law and Legislation for NHPs: "A law is the first stage of legislative procedures; it is a rule of conduct imposed by the authority" (WHO, 2005). It establishes the legal conditions under which NHPs should be organized in accordance with national policies (WHO, 2005). Here the indicators assigned measures the existence of various laws and legislations in selected nations required for the safe use of NHPs. All indicators were implemented by selected nations at the same level except for the indicator "The licensing or Registration system for NHPs" (see Table 4.2.2). Most of the countries implement different license or register schemes for NHPs based on their medicinal and non-medicinal claims. The medicinal claim NHPs have the intention to treat or prevent disease, correct or modify physiological function whereas non-medicinal claim NHPs are used to supplement the diet or to maintain/promote the health (WHO, 2005; Harrison, 2008). Australia and Germany were the only two countries implementing the licensing or registration system for both medicinal and non-medicinal claim NHPs whereas other countries implemented such system only for medicinal claimed NHPs (Harrison, 2008). All nations established national legislation

Attribute 2. Regulations for NHPs Manufacturers/Licenser: The NHPs regulations are vital for ensuring the safety, quality and efficacy of herbal medicines. Weak regulation and quality control may result in a high incidence of adverse reactions (WHO, 2003; WHO, 2005). In some nations, there are stricter regulatory requirements on medicinal claim NHPs manufacturers than the non-medicinal claimed NHPs. As shown in Table 4.1.2, none of the countries require proof of quality and efficacy from manufacturers for both medicinal and non-medicinal claim NHPs except Germany. In Germany, a special committee on herbal remedies called "Commission E" evaluate the quality and effectiveness of all herbal products (Liu & Salmon, 2010). Except New Zealand, all countries perform safety evaluations of NHPs prior to the marketing and impose obligations on manufacturers to adhere to GMP practices. In New Zealand, the safety requirements and GMP rules only apply to those herbal medicines claim to cure or help a disease (Ministry for Primary Industry, 1985; New Zealand Food Safety Authority, 2009).

Country	Attribute 1: Law and Legislation for NHPs					Attribute 2: Regulatory Requirements for NHPs manufacturers/Licensors				
	A national legislation for regulations of NHPs	The licensing or Registration system for NHPs	The law on control of NHPs advertisements	The legal status given to NHPs for sale in the market based upon medicinal/non-medicinal claims	Total Attribute Score	The requirement of providing proof of quality and efficacy	The safety evaluations of NHPs prior to marketing	The obligations on manufacturers to adhere to GMP practices	The labelling specifications for NHPs	Total Attribute Score
Australia	2	2	2	2	8	1	2	2	2	7
Germany	2	2	2	2	8	2	2	2	2	8
New Zealand	2	1	2	2	7	1	1	1	2	7
United Kingdom	2	1	2	2	7	1	2	1	2	6
United States	2	1	2	2	7	1	2	2	2	7
Rating Scale	2= Already Exist 1= In development 0= doesn't exist	2= For Both (medicinal and non-medicinal claim NHPs) 1= only for medicinal claim NHPs 0= not required		2= As prescription and over the counter products 1= only as the over the counter products 0= No restriction		2= For Both (medicinal and non-medicinal claim NHPs) 1= only for medicinal claim NHPs 0= not required				

Medicinal Claim NHPs: In most of the countries, NHPs are classified as medicinal claim/high risk NHPs if they intended to have therapeutic or prophylactic indications, and specified to treat, cure or prevent a disease or restore, correct or modify physiological functions ((WHO, 2005).
Non-medicinal Claim NHPs: NHPs classified as non-medicinal claimed/dietary supplements/ low risk if carries a specific health benefit and used to supplement the diet . The main purpose of these products is to maintain/promote the health (WHO, 2005; Harrison, 2008).

Table 4.1.2: Scores of Selected Countries for "Laws and Regulation for NHPs"

4.1.3 Sources of NHPs Adverse Reaction Information

This specific dimension refers to collection and collation of all reports of suspected adverse reactions associated with NHPs.

Attribute 1. Surveillance approaches: The surveillance approaches are defined as techniques to collect data for the purpose of detecting adverse effects after a medicinal product has been given a market authorization by a regulatory body (Aronson, 2012). There are mainly two surveillance approaches, i.e., active and passive. Table 4.1.3 shows that a passive surveillance system for NHPs exist in all nations but none of the country implemented the active surveillance method to collect NHPs adverse reaction information. Although United Kingdom, New Zealand, Germany and United States use several active surveillance approaches such as registries, intensive monitoring program, sentential sites etc. but only for therapeutic products and haven't utilized these methods specifically for NHPs or herbal medicines (Gering, & Sickmüller, 2005).

Attribute 2. Other Sources: The regulatory authorities collect NHPs adverse reaction information from multiple sources to increase their ability to detect rare NHPs adverse reactions. These multiple sources contribute in increasing the quality and quantity of adverse reaction information, and in strengthening the reporting systems already in place (WHO, 2003; WHO, 2004). In US, Poison Control centers are one of the major groups involved in reporting and assessment of dietary supplements adverse events whereas UK was the only country established link with several herbal-sector organisations such as National Institute of Medical Herbalist (NIMH) and Register of Chinese Herbal Medicine (RCHM) to collect NHPs AR reports

(Gardiner et al. 2008; Barnes, 2003). These organisations requests its members to report suspected ARs associated with herbal medicines and forward them to MHRA (Barnes, 2003). The implementation of these two distinct sources to collect NHPs adverse reaction information leads United Kingdom and United States score highest among all other nations. In all countries, manufacturers are responsible to collect NHPs AR information from three sources, i.e., foreign adverse reaction reports, literature scan and internet digital media except Germany. Germany's regulatory agency (BfArM) does not expect its manufactures to screen the internet regularly for adverse reactions associated with the use of their products (Liu & Salmon 2010).

Country	Attribute 1: Surveillance Approaches			Attribute 2: Other Sources				
	Existence of Passive surveillance system for NHPs	Implementation of Active surveillance system for NHPs	Total Attribute Score	A system in place to collect NHPs adverse reaction information from National Poison control center (PCC)	The Collection of AR reports from Herbal medicine practitioner/Organization	The provision of using WHO database and pool/access the AR information	The Information collected from Foreign adverse reaction reports, Literature scan and Internet digital media through manufacturers	Total Attribute Score
Australia	2	0	2	0	0	2	2	4
Germany	2	0	2	0	0	2	1	3
New Zealand	2	0	2	0	0	2	2	4
United Kingdom	2	0	2	0	2	2	2	6
United States	2	0	2	2	0	2	2	6
Rating Scale	2= Already Exist 1= In development 0= doesn`t exist			2= Already Exist 1= In development 0= doesn`t exist			2= Include all sources 1= at least two sources 0= one source or none	

Table 4.1.3: Scores of Selected Countries for "Sources of NHPs Adverse Reaction Information

4.1.4 Reporting of Adverse Reactions to Pharmacovigilance Centres

The countries are required to implement technologies, standards and tools that facilitate consumers and healthcare professionals to report their complaints regarding any marketed health products.

Attribute 1. Reporting Tools: The reporting tools include the various mediums through which public can easily submit or send adverse reaction forms to the pharmacovgilance centres. The Table 4.1.4 shows that Australia is the only country that distributes reporting forms to all doctors, dentists and pharmacists at a very frequently level i.e., four times/year, United Kingdom (UK) distributes at the frequent level, i.e., two time/year whereas other nations are not involved in this practice. Both nations (Australia and UK) distributes these AR reporting forms with each issue of the national adverse drug reactions bulletin along with the instructions/guidance on how to fill the form (Aagaard, Stenver & Hansen, 2008; Goundrey-Smith, 2008). All countries have done simple modifications in their national reporting forms to capture adverse reaction information related to NHPs such as "Other medicine(s)/vaccine(s) taken at the time of

the reaction" but did not mention NHPs specifically (TGA, 2012 a; BfArM, 2010; MEDSAFE, 2001; FDA, 2013 a). By adding a separate section on NHPs in national reporting forms for requesting name of ingredients, labels or name/address of manufactures/distributers would help to identify the complex nature of herbal medicines producing ARs (Barnes, 2003).

Attribute 2. Reporting Requirements: For strengthening the pharmacovigilance activity in the non-prescription medicines setting, it is important to set reporting requirements for different groups such as healthcare professionals (HCP), manufacturers and consumers (Van Hunsel et. al., 2012). As shown in Table 4.1.4, most of the selected countries included healthcare professionals (HCP) and consumers as their national volunteer reporters whereas Germany accepts reports of observed adverse effects only from health professionals since the scientific assessment of reported events requires specialised medical information. Patients are required to ask a doctor to complete the reporting form (BfArM, 2010). All nations set obligatory requirements on manufacturers to report NHPs adverse reaction except United States (US). FDA asks its manufacturers to report ARs associate with NHPs only on volunteer basis (Frankos, Street, & O'Neill, 2010).

Country	Attribute 1: Reporting Tools						Attribute 2: Reporting Requirement		
	The existence of facility of Reporting via Telephone, email, Fax and post to consumers and HCP	The Provisions of Electronic /online Reporting to consumers and HCP	Periodic distribution of Reporting Forms to all HCP	Distribution of reporting forms to herbalist/ herbal organisations	Modifications in National AR reporting form to cover NHPs	Total Attribute Score	Includes HCP and consumers as recognised reporters by national ARs reporting scheme	The requirements on manufacturers to report NHPs ARs to regulatory authorities	Total Attribute Score
Australia	2	2	2	0	1	7	2	2	4
Germany	2	2	0	0	1	5	1	2	3
New Zealand	2	2	0	0	1	5	2	2	4
United Kingdom	2	2	1	0	1	6	2	2	4
United States	2	2	0	0	1	5	2	1	3
Rating Scale	2= Already Exist 1= In development 0= doesn`t exist		2=Very Frequent (3-4 times/year) 1=Frequent (1-2 times/ year) 0=not at all	2=Very Frequent (3-4 times/year) 1=Frequent (1-2 times/ year) 0=not at all	2= Adding separate section for NHPs in national AR form 1=Simply Modified reporting form 0=No changes		2= Both 1=Only HCP 0= None	2=Obligatory reporting 1=Volunteer reporting 0=not required	

- **Adding separate section for NHPs in national AR Form:** By adding a separate small section on NHPs in national reporting form, the important detail on herbal medicines can be requested such as listing ingredients, labels or name/address of manufactures/distributers which are helpful to identify the complex ingredients of herbal medicines producing ADR (Barnes, 2003).
- **Simply Modified Reporting Form:** In most of the countries, simple modifications were done to national reporting form by adding a sub-section such as "Adverse reaction for other drugs" or "Other medicine(s)/NHPs/vaccine(s) taken at the time of the reaction".
- **Obligatory Reporting**: it means that manufacturers are legally obliged to report any serious, unexpected or suspected case of AR or interaction or misuse of NHPs
- **Volunteer Reporting**: There is no legal responsibility of manufacturers to report AR regarding NHPs

Table 4.1.4: Scores of Selected Countries for "Reporting of NHPs Adverse Drug Reaction to Pharmacovigilnce Centre"

4.1.5 Data Management and Assessment of Case Reports

This dimension refers to managing adverse reaction information and assessing that data using particular standards. It is categorised into two attributes, the first one is called as Data Management and the second is Assessment of Case Reports. Following is the brief description of selected countries implementing Data Management and Assessment of Case Reports tools.

Attribute 1. Data Management: This attribute refers to the requirement of database and technology which organises information in a way to ensure the quality and integrity of the data collected (ICH, 2003). The table 4.1.5 presents the score given to each country according to the degree of implementation of each indicator. Most of the selected international jurisdictions implemented all indicators at the optimum level except Australia and New Zealand. In both of these countries, the electronic exchange of AR reports between manufacturers and regulatory authorities according to the standards of ICH-E2B have not been implemented yet **(**MEDSAFE, 2013; Aagaard, Stenver & Hansen, 2008). The other nations set up a data network according to the ICH-E2B standards which is used to accept ARs reports electronically from manufactures to facilitate direct database-to-database transmission (MHRA, 2013b ; FDA, 2012 c; BfArM, 2012; Mann & Andrews, 2002).

Attribute 2. Assessment of Case Reports: This specific attribute refers to the standards, skills and expertise required to assess the case reports for finding out the important relationships between NHPs and adverse reactions (WHO, 2000). As shown in table 4.1.5, Australia and New Zealand implemented all the indicators and attained highest score. These were the only two nations who provide personalized feedback for each reported AR to the reporters. All other countries only acknowledge the receipt of report through a letter of confirmation and/or information about what will happen to the report along with a new AR reporting form (Van Hunsel et al. 2012). The Australian Government established an AME line, a phone-in service that encourages public to report and discuss side effects, specifically for providing personalized feedback to each reporter and discuss side effects (Mackay, 2005). Worldwide, New Zealand demonstrate itself for establishing an effective routine procedure through personalized feedback letters are sent to the reporters from the pharmacovigilance centres. This feedback typically consists of the centre's causality assessment, the number of similar reports in NZ and/or WHO, plus any other additional information (Van Hunsel et al. 2012).

Country	Attribute 1: Data Management						Attribute 2: Assessment of Case Reports					
	Use of MedDRA for Coding of NHPs Adverse Reaction	Availability of technology for the electronic Exchange of ARs reports between MAH and regulatory authorities	A Mechanism in place to check integrity, completeness and duplicates of AR reports	A system to conduct Follow-up actions	A national legislation on keeping confidentiality and Security of reporter's identity and information	Total Attribute Score	Use of WHO causality categories for assessing case reports	Use of Signal Detection Technique	The assessment of reports done in cooperation with an expert panel	Provisions of personalized feedback to reporters	Acknowledgement given to the reporters on receipt of each report	Total Attribute Score
Australia	2	0	2	2	2	8	2	2	2	2	2	10
Germany	2	2	2	2	2	10	2	2	2	0	2	8
New Zealand	2	0	2	2	2	8	2	2	2	2	2	10
United Kingdom	2	2	2	2	2	10	2	2	2	0	2	8
United States	2	2	2	2	2	10	2	2	2	0	2	8
Rating Scale	2= Already Exist 1= In development 0= doesn't exist						2= Already Exist 1= In development 0= doesn't exist					

Acknowledgment: Acknowledgement is a quick confirmation of the receipt of the report. According to WHO (2004), a new reporting form should be supplied to the reporter as well as links to the electronic monthly bulletin, Drug Safety Updates

Feedback: The personalized feedback is further information than just acknowledgment. The feedback consist of receiving additional information about the reaction concerned such as the number of similar reports in a country and/or WHO, plus any other information about the reported association. Such feedback will motivate the reporter to send in further reports (WHO, 2004; Van Hunsel et al. 2012)

Table 4.1.5: Scores of Selected Countries for "Data management and Assessment of Case Reports"

4.1.6 Risk Minimization and Communication

The risk minimization and communication refers to taking preventive action and timely communication among stakeholders such as patients/consumers, healthcare professionals (HCP), manufacturers, and international regulatory bodies. This dimension was categories to two attributes: Risk Minimization Activities and Risk Communication Sources.

Attribute 1. Risk Minimization Activities: The risk minimization activities refer to the implementation of various regulations, resources and actions taken to prevent the risk that could occur after post-authorization of health products. Only few countries have implemented the requirement of Risk Management Plans (RMPs) and periodic submission of summary reports from NHPs manufacturers (see Table 4.1.6 for details). The RMPs provide a comprehensive review of important identified risks of the product , potential risks, and missing information whereas summary reports are intended to give an update of the worldwide safety experience of a product to Competent Authorities at defined time points post-authorisation including all ARs reported in the period since the last summary report, review of the registration status of the product worldwide, actions taken for safety reasons, the worldwide usage of the product and an analysis of safety product (EMA, 2012 a). Only Germany and United Kingdom (UK) set the requirement on NHPs manufacturers for submitting RMPs for any initial marketing authorisation applications and periodic submission of summary reports in PSURs format (i.e. every 6 months for the

first 2 years of marketing, then yearly and then every 3 years.). These requirements are exempt for those NHPs which fall within the scope of the traditional-use registration, i.e., NHPs have the evidence of traditional use of at least 30 years, including at least 15 years in the Europe (EMA, 2012 a; MHRA, 2013e).

Attribute 2. Risk communication Tools: The risk communication is an interactive process of exchanging information and opinion on risk among various stakeholders (WHO, 2013). The indicators assigned to this specific attribute determine the implementation of various tools required to disseminate adverse risk information effectively to target audience in selected nations. As shown in table 4.1.6, all the indicators were implemented by selected countries at the same level except the indicator "A bulletin or newsletter periodically distributed to healthcare Professionals". This indicator was measured at the rating scale from "very frequent" to "less frequent". Australia was the only country which publishes and distributes a newsletter called Australian Adverse Drug Reactions Bulletin at "very frequent" level i.e. six times a year (Boyd, 2002) whereas all other nations disseminate their adverse reaction bulletin at a "frequent" level i.e three to four time a year (McEwen, 2004; MHRA, 2013 d). Other than that, all nations regularly update their regulatory websites for announcements regarding important safety information such as product withdraws, warnings, recalls etc . and send "Dear Doctor Letter" to alert health professionals in case of safety issues (MHRA, 2013 d; Mann & Andrews, 2002; Amor, 2010; Harvey, 2010; MEDSAFE, 2012 b ; FDA, 2013 c). Also, these nations provide information regarding NHPs to their consumers through variety of sources. For example In US, the information about NHPs is provided by Ministry of Health provides through Medsafe website, special interest and lobby groups (eg, Citizens for Health Choices), government bodies (eg, the Ministry of Consumer Affairs) health information websites and consumer health magazines (eg, Healthy Options) (MACCAM, 2005).

Country	Attribute 1: Risk Minimization Activities					Attribute 2: Risk Communication Sources				
	A system in place to educate health care professionals on reporting and new adverse reaction issues	Provisions of tracking urgent/general international safety concerns	Regulatory authorities requiring Risk Management Plans (RMP) from NHPs manufacturers	Regulatory authorities requiring summary reports from NHPs manufacturers	Total Attribute Score	A bulletin or newsletter periodically distributed to healthcare Professionals	Provisions of website announcements to consumers and HCP regarding product withdraw, Recalls, and safety warnings	Sending "Dear Health Professional Letters`` in urgent safety issues	Availability of consumer's NHPs information sources	Total Attribute Score
Australia	2	2	0	1	5	2	2	2	2	8
Germany	2	2	2	2	8	1	2	2	2	7
New Zealand	2	2	0	0	4	1	2	2	2	7
United Kingdom	2	2	2	2	8	1	2	2	2	7
United States	2	2	0	0	4	1	2	2	2	7
Rating Scale	2= Already Exist 1= In development 0= doesn't Exist			2= Periodic submission 1= only upon demand 0= not required		2= Frequent (5-6 times/year) 1= less Frequent (2-4) times/year) 0= 1 or less than 1)	2= Already Exist 1= In development 0= doesn't Exist			

Periodic submission: The manufacturers are required to submit summary reports to regulatory authorities at specific intervals of time
Only upon demand: The manufacturers submit summary reports in specific conditions only upon demand by regulatory authorities

Table 4.1.6: Scores of Selected Countries for "Risk Minimization and Communication"

4.2 Identification of Best-Practices

Implementing a well-functioning NHP post-market surveillance system is a dynamic process and requires proper resources as well as established standards to follow. In this section, the appropriate and feasible NHPs post-market surveillance practices identified through comparative analysis of selected nations and referred here as best practices. For each attribute of the reference framework, only the countries that scored highest in comparative analysis were chosen to contribute best practice elements.

Table 4.2 shows the list of identified evidence based best practices and highest scored countries executing best practices for the each attribute of a dimension. Also, the table depicts the best practices scores. A best practice score for each attribute is the score of the highest scored country executing best practices. Although each selected nation contributed to best practices as every country holds its unique strengths and features in implementing different attributes but Australia and United Kingdom contributed maximum in formulation of best practices. Overall, these both nations appeared most often as highly scored nations in attributes, followed by Germany whereas New Zealand and United States contributed the least. The implementation of maximum number of indicators at their highest level leads Australia and United Kingdom to score highest in most of the attributes.

The grouping of best practices was made into "core" and "supplementary" components (as shown in Table 4.2). For example, the first attribute of Dimension 1 "Structure Elements", it is noted that Australia, United Kingdom (UK) and United States (US) achieved highest scores (scores of 8 points) in the comparative analysis, and thus each contributed to best practices. Here all indicators were commonly implemented across these three countries so all derived best practices were considered as "core".

Consider the example for attribute "3.2. Other Sources", in which the United Kingdom (UK) and United States (US) supplied evidence, based best practices by scoring highest (scores of 6 points). The two distinct groups of best practices were formulated, i.e., core and supplementary. The core practices were indicators which were commonly followed by both highly scored nations, and the supplementary practices were those indicators which were uncommonly or uniquely followed by both nations, i.e., collection of NHPs adverse reaction information from a Poison Control Centre (PCC) and collection of NHPs adverse reaction reports from herbal medicine practitioner/organisation.

Dimension	*Attributes*	*Highest Scored Countries Executing Best Practices*	*Evidence Based Best Practices*	*Best Practices Score*
1. NHPs post-market surveillance system structure and stakeholder coordination	1.1 Structure Elements	• Australia • UK • US	**Core Best Practices** • The existence of a regulatory agency or relevant department for NHPs • The Presence of a national pharmacovigilance centre including NHPs in their current scope • Existence of a expert advisory committee on safety of NHPs • Presence of a national research Institute for NHPs	**8**
	1.2 Coordination and Collaboration of stakeholders	• Australia • UK	**Core Best Practices** • Frequent meetings of advisory committee members (5-6 times/year) • Collaboration with both WHO and foreign national monitoring centres	**4**
2. Laws and Regulation for NHPs	2.1 Law and Legislation for NHPs	• Australia • Germany	**Core Best Practices** • The existence of a national legislation for regulations of NHPs • The licensing/Registration requirements for both medicinal and non-medicinal claim NHPs • The law on control of NHPs advertisements for medicinal/ non-medicinal claim NHPs • The legal status given to NHPs for sale in the market based upon medicinal/non-medicinal claims as over the counter and prescription products	**8**
	2.2 Regulations for NHPs manufactures	• Germany	**Core Best Practices** • The requirement of providing proof of quality and efficacy from manufacturers for medicinal/non-medicinal claim NHPs • The safety evaluations of NHPs prior to marketing for medicinal/ non-medicinal claim NHPs • The obligation on manufacturers to	**8**

Dimension	*Attributes*	*Highest Scored Countries Executing Best Practices*	*Evidence Based Best Practices*	*Best Practices Score*
			adhere to GMP practices for medicinal/non-medicinal claim NHPs • The Labelling specifications for NHPs manufacturers for medicinal/ non-medicinal claim NHPs	
3. Sources of NHPs Adverse Reaction Information	3.1 Surveillance Approaches	• Australia • Germany • NewZealand • UK • US	**Core Best Practices** • The Existence of Passive surveillance system for NHPs	**2**
	3.2 Other sources	•UK •US	**Core Best Practices** • Provision of using WHO database and pool/access the AR information • The Information collected from Foreign adverse reaction reports, Literature scan and Internet digital media through manufacturers **Supplementary Best Practices** • A system in place to collect NHPs adverse reaction information from National Poison Control Centre (PCC) **or** • The Collection of AR reports from Herbal medicine practitioner/Organization	**6**
4. Reporting of NHPs adverse reactions to Pharmacovigilance Centre	4.1 Reporting Tools	• Australia	**Core Best Practices** • The existence of facility of reporting via Telephone, email, fax and post to consumers /HCP • The Provisions of Electronic /online Reporting to consumers and healthcare professionals (HCP) • Periodic distribution of reporting forms to all health care professionals (3-4 times/year) • Modifications in national AR reporting forms to cover NHPs	**7**

Dimension	*Attributes*	*Highest Scored Countries Executing Best Practices*	*Evidence Based Best Practices*	*Best Practices Score*
	4.2 Reporting Requirements	• Australia • New Zealand • UK	**Core Best Practices** • Including HCP and consumers as recognised reporters by national ARs reporting scheme • The obligatory reporting requirements for manufacturers to report NHPs adverse reaction to regulatory authorities.	**4**
5. Data Management and Assessment of Case Reports	5.1 Data Management	• Germany • UK • US	**Core Best Practices** • Use of MedDRA for coding of NHPs adverse reaction (ARs) • Availability of technology for the electronic exchange of ARs reports between MAH and regulatory authorities according to ICH standards • A Mechanism in place to check integrity, completeness and duplicates of AR reports • A system to conduct Follow-up actions when the information is incomplete • A national legislation on keeping confidentiality and Security of reporter's identity and information	**10**
	5.2 Assessment of case reports	• Australia • New Zealand	**Core Best Practices** • Use of WHO causality categories for assessing case reports • Use of Signal Detection Techniques such as PRR, Bayesian methods and others • The assessment of reports done in cooperation with an expert panel comprising experts in multidisciplinary areas • Provisions of personalized feedback to the reporters • Acknowledgement given to the reporters on receipt of each report	**10**

Dimension	*Attributes*	*Highest Scored Countries Executing Best Practices*	*Evidence Based Best Practices*	*Best Practices Score*
6. Risk Management and Communication	6.1 Risk Minimization Activities	• Germany • UK	**Core Best Practices** • A system in place to educate health care professionals on reporting and new adverse reaction issues • Provisions of tracking urgent/general international safety concerns • Regulatory Authorities Requiring Risk Management Plans (RMPs) from NHPs manufacturers • Regulatory Authorities requiring periodic submission of summary Reports from NHPs manufacturers	**8**
	6.2 Risk Communication Tools	• Australia	**Core Best Practices** • A bulletin or newsletter periodically distributed to healthcare Professionals (5-6 times/year) • Provisions of website announcements to consumers and HCP regarding product withdraw, Recalls, and safety warnings • Sending "Dear Health Professional Letters" in urgent safety issues • Availability of consumer's NHPs information sources	**8**

Table 4.2: Evidence Based Best Practices

Chapter 5: Critical Analysis of the Canadian NHP Surveillance System

The objectives of this chapter were to measure Canadian surveillance system in quantitative form and to compare it with best practices to identify the gaps. This chapter was divided to two sections: Section 5.1 Description of Canadian NHPs surveillance framework, and Section 5.2 Gaps in Canadian Surveillance System in comparison to Best Practices. The objective of Section 5.1 is to score the Canadian surveillance system based on comparison against the reference framework indicators, and analyse it against the best practices scores to identify key gaps. Section 5.2 focuses on the gaps between the Canadian surveillance system and best practices for NHPs post-market surveillance.

5.1 Description and Scoring of Canadian NHPs Surveillance Framework

In this section, the findings on Canadian NHPs post-market surveillance system components are presented and compared with the reference surveillance framework. The comparative analysis is conducted by assigning a numeric value to Canadian system according to implementation of each reference framework indicator. This analysis was performed within each attribute of a dimension and the total attribute score is measured for the Canadian surveillance system. The sections below and Tables 5.1.1 to 5.1.6 present the dimension by dimension indicator scores for the Canadian Surveillance system and best practices both to depict where Canada attained less, equal or higher score than the international comparative analysis of best practices.

5.1.1 NHPs post-market surveillance system structure and stakeholder coordination

Attribute 1. Structure Elements: Canada has implemented all reference framework indicators required for a well-functioning NHP surveillance system structure (as shown in Table 5.1.1). Health Canada is the regulatory body responsible for approving drugs and NHPs for marketing in Canada. The Natural Health Product Program, part of Health Canada, includes Natural Health Product Directorate (NHPD), Marketed Health Product Directorate (MHPD), and Health Products and Food Branch Inspectorate. NHPD control and manage the NHP regulations which specify the requirements for the manufacturers with regards to packaging, labelling, storage, distribution and sale of NHPs in Canada; "MHPD is responsible for coordination and consistency of post-marketing surveillance, assessment of signals and safety trends for all marketed health products whereas Health Products and Food Branch Inspectorate is in charge for "branch-wide compliance and enforcement activities, enabling consistency of approach across the spectrum of regulated products" (Health Canada, 2013 June, p.2). The Canadian pharmacovigilance center is called as Canada Vigilance Program which collects and assesses reports of NHPs along with other medicines (Harrison, 2008). An expert group called Natural Health Products Program Advisory Committee (NHPPAC) is formed to provide the Natural Health Products Program timely advice and

recommendations on NHPs safety issues (Health Canada, 2012 April). Another important group called Expert Advisory Committee on the Vigilance of Health Products (EAC-VHP) gives the Health Products and Food Branch of Health Canada an expert advice on broad strategic policy issues related to the safety of health products including drugs, biologics, NHPs and medical devices (Health Canada, 2007 April). There are several national research Institutes established in Canada that focus specifically on NHPs such as the Research Centre for Alternative Medicine in Calgary, the Tzu Chi Institute for Complementary and Alternative Medicine in Vancouver etc.(MACCAM, 2003; WHO, 2005)

Attribute 2. Coordination and collaboration with stakeholders: The Natural Health Products Program Advisory Committee (NHPPAC) and Expert Advisory Committee on the Vigilance of Health Products (EAC-VHP) members meets face to face two times /year and discuss NHPs issues for assuring the safety, quality and efficacy of NHPs for sale in Canada (Health Canada, 2012 April). Canada is active member of WHO medicine safety program and regularly submits the AR reports to the WHO global ICSR database (UMC, 2013). Also, Canada shares ongoing federal regulatory post-market surveillance/vigilance issues by collaborating with foreign national monitoring centres through Memoranda of Understanding (MOU) and conducts a regular video/teleconference with federal regulatory partners in the United States, New Zealand and Australia (Health Canada, 2004 October).

Country	Attribute1: Structure Elements					Attribute 2: Coordination and collaboration with stakeholders		
	A regulatory agency or relevant department for NHPs	A National Pharmacovigilance Center covering NHPs in their scope	Existence of a Expert Advisory committee on safety of NHPs	Presence of National research Institute for NHPs	**Total Attribute Score**	Frequent Meetings of advisory committee	Collaboration with WHO and Other National Monitoring Centers	**Total Attribute Score**
Canada	2	2	2	2	**8**	1	2	**3**
Best Practices Score					**8**	**Best Practices Score**		**4**
Rating Scale	2= Already Exist 1= In development 0= doesn't exist					2=Very Frequent (5-6 times/ year) 1 = Frequent (2-4/year) 0= less frequent (only 1/year)	2= Collaborations with WHO and national monitoring centers 1= Collaborations with only WHO 0= None	

Already Exist: A system, rule , technology or element that has implemented in a country and currently in a functional form
In development: A system, rule or element that is in the process /development or in plan of implementation and not yet in its functional form
Doesn't Exist: A system, rule or element that is not implemented nor in the development process

Table 5.1.1: Scores of Canada for "System structure and stakeholder coordination"

5.1.2 Laws and Regulations for NHPs

Attribute 1. Law and Legislation for NHPs: As shown in table 5.1.2, Canada implemented all the reference framework indicators required for the proper functioning of the given attribute. In Canada, a national legislation was established for NHPs which includes herbs or botanicals and regulated under the Natural Health Products Regulations (NHPR). These regulations address the unique nature of NHPs which are distinct from food and drugs (Jordan et al. 2010). The licensing or registration requirements for NHPs apply to any person or company that manufactures, packages, labels and/or imports NHPs for commercial sale in Canada. These requirements are established for all classes of NHPs such as medicinal and non-medicinal ingredient NHPs (Harrison, 2008). In Canada, the legal status given to NHPs for sale in Canadian market as prescription and over-the-counter products based upon their medicinal ingredients, source, dose, potency, non-medicinal ingredients and recommended use(s) (Health Canada, 2012 December). The Food & Drugs Act regulates the advertising of food and drug products. The act prohibits misleading advertising to the general public for unapproved claims or claims that are not in the labelling standards of all classes of NHPs (NHPD, 2010)

Attribute 2. Regulations for NHPs Licenser: The regulations for NHPs licensor is a pre-market system where each NHP receive market authorisation by obtaining a product licence based on evidence that the product is safe under the recommended conditions of use without a prescription, effective for the proposed claims, and of high quality (Jordan et al 2010). Canada has imposed all the required regulations on NHPs manufacturers or licensor which maximize the safety and quality of NHPs prior to launch and throughout the life cycle of product in market. Canada obtained maximum points for each reference framework indicator (shown in table 5.1.2).These are requiring evidences of quality, safety and efficacy prior to license from manufactures, obligations on adherence to GMP rules for manufacturing NHPs, and labelling specification (NHPD, 2010).

Country	Attribute1: Law and Legislation for NHPs					Attribute 2: Regulatory Requirements for NHPs manufacturers/Licensors				
	A national legislation for regulations of NHPs	The licensing or Registration requirements for NHPs	The regulation on control of NHPs advertisements	The legal status given to NHPs for sale in the market based upon medicinal/non-medicinal claims	**Total Attribute Score**	The requirement of providing proof of quality and efficacy	The safety evaluations of NHPs prior to marketing	The obligations on manufacturers to adhere to GMP practices	The Requirements on Labelling of NHPs	**Total Attribute Score**
Canada	2	2	2	2	8	2	2	2	2	8
Best Practices Score					8	**Best Practices Score**				8
Rating Scale	2= Already Exist 1= In development 0= doesn't exist	2= For Both (medicinal and non-medicinal claim NHPs) 1= only for medicinal claim NHPs 0= not required		2= As prescription and over the counter products 1= only as the over the counter products 0= No restriction		2= For Both (medicinal and non-medicinal claim NHPs) 1= only for medicinal claim NHPs 0= not required				
Medicinal Claim NHPs: In most of the countries, NHPs are classified as medicinal claim/high risk NHPs if they intended to have therapeutic or prophylactic indications, and specified to treat, cure or prevent a disease or restore, correct or modify physiological functions ((WHO, 2005). **Non-medicinal Claim NHPs:** NHPs classified as non-medicinal claimed/dietary supplements/ low risk if ut carries a specific health benefit and used to supplement the diet . The main purpose of these products is to maintain/promote the health (WHO, 2005; Harrison, 2008).										

Table 5.1.2: Scores of Canada for "Laws and Regulations for NHPs"

5.1.3 Sources of NHPs Adverse Reaction Reports

Attribute 1. Surveillance Approaches: Canada has implemented passive surveillance system in form of a spontaneous reporting system. The AR reports are submitted voluntarily by health professionals, consumers and caregivers to seven regional AR centers (BC, AB, SK, MB, ON, QC, and Atlantic) as well as directly to the national office of Canada Vigilance, which are inputted into the Canada Vigilance database (Wiktorowicz et al., 2008). A comprehensive pharmacovigilance system requires both passive and active approaches in order to evaluate potential problems as well as provide measures for potential risks (ICH, 2005). Canada uses a number of active approaches to monitor the safety of prescription drugs such as record linkage system but currently no active surveillance approach is in use to collect adverse reactions regarding NHPs (WHO, 2002).

Attribute 2. Other Sources: In Canada, there is lack of implementing a formalized system to routinely utilize NHPs adverse reaction information from Canadian Poison Control Centers (PCC) to detect potential signals. Although some projects are conducted to explore the utility of this source such as a three year collaborative projects between NHPD and the Ontario Poison Center and the British Columbia Drug and Poison Information Centre but still limited to pilot studies level (Health Canada, 2012, March). The Canada Vigilance Program accepts reports from all practitioner types, including herbal medicine practitioners, as part of the passive, voluntary reporting structure but Health Canada haven't establish a

scheme to routinely collect NHPs ARs from herbal medicine practitioner or national herbal organisations such as Ontario Herbalist Association, The Canadian Council of Herbalist Associations (CCHA) etc. These organisations can be a valuable source for collecting NHP AR by requesting its members to report suspected ARs associated with herbal medicines and forward them to Health Canada. Canada is active member of WHO medicine safety program and has the provision of using WHO database as a reference source for signal strengthening and receive WHO publication newsletters, guidelines and books in the pharmacovigilance and risk management area (WHO, 2013). In Canada, it is the responsibility of Market Authorization Holders (MAHs) to report all serious domestic and serious foreign unexpected adverse reaction reports to the regulatory agency in an expedited fashion, i.e., 15 calendar days of receiving the relevant information. It is also an expectation that MAHs screen the worldwide scientific literature on a regular basis and internet or digital media in order to check any significant safety issues which may necessitate reporting (Health Canada, 2011 March).

Country	Attribute1: Surveillance Approaches		Total Attribute Score	Attribute 2: Other Sources				Total Attribute Score
	Existence of Passive surveillance system for NHPs	Implementation of Active surveillance system for NHPs		A system in place to collect NHPs ARs information from Poison control center (PCC)	The Collection of AR reports from Herbal medicine practitioner/Organization	provision of using WHO database and pool/access the AR information	The Information collected from Foreign adverse reaction reports, Literature scan and Internet digital media through manufacturers	
Canada	2	0	**2**	0	1	2	2	**5**
Best Practices Score			**2**	**Best Practices Score**				**6**
Rating Scale	2= Already Exist 1= In development 0= doesn`t exist			2= Already Exist 1= In development 0= doesn`t exist			2= Include all sources 1= at least two sources 0= one source or none	

Table 5.1.3: Scores of Canada for "Sources of NHPs Adverse Reaction Reports"

5.1.4 Reporting of Adverse Reactions to Pharmacovigilance Centres

Attribute 1. Reporting Tools: As a regular practice, Health Canada doesn't distribute adverse reaction reporting forms to health care professionals or to herbalist/ herbal organisations. Although, in March 2013, AR reporting forms were distributed to selected health associations, physicians and pharmacist but this practice is not accepted as a periodic or regular like other countries such as Australia and United Kingdom (Health Canada, 2011 January; NHPD, 2013). In Canadian AR reporting form, a section called "About the health product that may have caused the side effect" specifically mentions that health product also includes natural health products. Apart from that, the Canadian reporting form consists of a separate section for NHPs which record important details on NHPs such as name of herbal ingredients,

manufacturers or copy of labels (Health Canada, 2011). This practice enables Canadian reporting forms to record important details on NHPs and found very rare in international reporting forms.

Attribute 2. Reporting Requirements: The Canadian reporting scheme includes healthcare professionals and consumers as recognised reporters as Canada values consumers and healthcare professionals experience and allow them to report adverse reaction reports directly either to Health Canada or to MAH as a way to improve pharmacovigilance without any obligation whereas the manufacturers are obliged to report serious adverse reactions to their product in an expedite manner, i.e., 15 days after receiving or becoming aware of the information (Health Canada, 2011, March).

Country	Attribute1: Reporting Tools						Attribute 2: Reporting Requirement		
	The existence of facility of Reporting via Telephone, email, Fax and post to consumers and HCP	The Provisions of Electronic /online Reporting to consumers and HCP	Periodic distribution of Reporting Forms to all HCP	Distribution of reporting forms to herbalist/ herbal organisations	Modifications in National AR reporting form to cover NHPs	Total Attribute Score	Inclusion of HCP, and consumers as recognised reporters by national ARs reporting scheme	The requirements on manufacturers to report NHPs adverse reaction to regulatory authorities	Total Attribute Score
Canada	2	2	0	0	2	6	2	2	4
Best Practices Score						7	**Best Practices Score**		4
Rating Scale	2= Already Exist 1= In development 0= doesn`t exist		2= Very Frequent (4-3 times/year) 1= Frequent (2-1 times/ year) 0= not at all	2= Very Frequent (4-3 times/year) 1= Frequent (2-1 times/ year) 0= not at all	2= Adding separate section for NHPs in national AR form 1= Simply Modified reporting form 0= No changes		2= Both 1= Only HCP 0= none	2= Obligatory reporting 1= Volunteer reporting 0= not required	

- **Adding separate section for NHPs in national AR Form:** By adding a separate small section on NHPs in national reporting form, the important detail on herbal medicines can be requested such as listing ingredients, labels or name/address of manufactures/distributers which are helpful to identify the complex ingredients of herbal medicines producing ADR (Barnes, 2003).
- **Simply Modified Reporting Form:** In most of the countries, simple modifications were done to national reporting form by adding a sub-section such as "Adverse reaction for other drugs" or "Other medicine(s)/NHPs/vaccine(s) taken at the time of the reaction".
- **Obligatory Reporting**: it means that manufacturers are legally obliged to report any serious, unexpected or suspected case of AR or interaction or misuse of NHPs
- **Volunteer Reporting**: There is no legal responsibility of manufacturers to report AR regarding NHPs

Table 5.1.4: Scores of Canada for "Reporting of Adverse Reactions to Pharmacovigilance Centres"

5.1.5 Data Management and Assessment

Attribute 1. Data Management: Canada uses the internationally recognized MedDRA terminology for the coding of adverse reactions reports submitted to the Canada Vigilance Program (Health Canada, 2010 November). Canada has implemented the technology for the electronic exchange of ARs reports between MAH and regulatory authorities according to ICH standards. "It includes both an electronic gateway for

large industry use and a web-based portal for small and medium sized manufacturers. Industry partners are currently being registered for the electronic gateway and the interface for the web-based portal has been developed" (Health Canada, 2013 April). AR reports are reviewed for integrity, completeness and duplicates for further processing. In Canada, the MAH are expected to collect follow-up information through telephone call, site visit or a written request (Health Canada, 2011 March). Information about the identity of the reporter, patient and the health care provider is kept confidential and protected as personal information under the Privacy Act (Health Canada, 2012 October).

Attribute 2. Assessment of Case Reports: Canada use the WHO defined causality categories in determining the casual relationship. Signals from the Canada vigilance database are identified through the systematic review of AR reports and periodic analysis with statistical tools (Health Canada, 2012 October). In Canada, there is no personalized feedback given to reporters on association between the drug and reported AR. The reporters are acknowledged with the receipt of AR reports and a new reporting form is supplied to the reporter along links to electronic monthly bulletin (Van Hunsel et al. 2012).The clinical and scientific staff members of Marketed Health product Directorate (MHPD) assess and review the AR reports, either as individual reports or as summary cumulative reports (Health Canada, 2012 October; Health Canada, 2011 March).

Country	Attribute1: Data Management						Attribute 2: Assessment of Case Reports					
	Use of MedDRA for Coding of NHPs Adverse Reaction	Availability of technology for the electronic Exchange of ARs reports between MAH and regulatory authorities	A Mechanism to check integrity, completeness and duplicates of AR reports	A system to conduct Follow-up actions	A national legislation on keeping confidentiality of reporter's identity	**Total Attribute Score**	Use of WHO causality categories for assessing case reports	Use of Signal Detection Techniques such as PRR, Bayesian methods and others	The assessment of reports with an expert panel	Provisions of personalized feedback to reporters	Acknowledgement given to the reporters on receipt of each report	**Total Attribute Score**
Canada	2	2	2	2	2	**10**	2	2	2	0	2	**8**
Best Practices Score						**10**	**Best Practices Score**					**10**
Rating Scale	2= Already Exist 1= In development 0= doesn`t exist						2= Already Exist 1= In development 0= doesn`t exist					
Acknowledgment: Acknowledgement is a quick confirmation of the receipt of the report. According to WHO (2004), a new reporting form should be supplied to the reporter as well as links to the electronic monthly bulletin, Drug Safety Updates **Feedback**: The personalized feedback is further information than just acknowledgment. The feedback consist of receiving additional information about the reaction concerned such as the number of similar reports in a country and/or WHO, plus any other information about the reported association. Such feedback will motivate the reporter to send in further reports (WHO, 2004; Van Hunsel et al. 2012)												

Table 5.1.5: Scores of Canada for "Data Management and Assessment of Case Reports"

5.1.6 Risk Minimization and Communication

Attribute 1. Risk Minimization activities: In this attribute, Canada implemented some but not all reference framework indictors shown in Table 5.1.6. Health Canada provides education to healthcare professionals through tools available on MedEffect Canada Website. In addition, Health Canada conducts outreach to various HCP groups nationally for AR reporting for all therapeutic products, however certain

outreach is geared towards NHP education specifically (e.g., to Canadian colleges of naturopathic medicine) (NHPD, 2013; Health Canada, 2009 February). Health Canada tracks urgent /general international safety concerns by developing several bilateral international agreements with various foreign agencies which allow continuous sharing of information through various collaborative efforts (NHPD, 2013; Health Canada, 2004 October). Health Canada doesn't requires Risk Management Plans (RMPs) from NHPs manufacturers. Although Health Canada receives RMPs from pharmaceutical, biologic and biotechnology-derived products upon demand in case of safety issues emerge but not for NHPs (MedEffect Canada, 2012; Health Canada, 2009 February; Health Canada, 2011, November). In Canada, NHPs manufacturers have to prepare a summary report in Periodic Benefit-risk Evaluation Report (PBRER) or Periodic safety update report (PSUR) format (these are recommended format for summary reports according to ICH standards) (Health Canada, 2013, April 10). There is no regulatory requirement on NHPs manufacturers to submit summary report but provided only upon request by Health Canada if the safety and/or effectiveness of a health product is/are warranted (Jordan et. al. 2009; Health Canada, 2011, March 17).

Attribute 2. Risk Communication Tools: Canada publishes and distributes its Adverse Reaction bulletin four to five times a year to physicians, pharmacists, other health professionals and interested parties by mail. Health Canada post and distribute risk communications on the MedEffect™ Canada Web site which regularly provide Health Canada's warnings, recalls , advisories, foreign product alerts and information updates for health products that Canadians use every day (MedEffect Canada, 2007 August; Health Canada, 2011 April). Health Canada develops "Dear Healthcare Professionals" letters to educate health care professionals about new and important drug information and sends immediate safety concerns through emails, postal mails and fax. Consumers in Canada currently have access to a variety of information on NHPs such Health Canada's website which includes information on Natural Health Products, public health agency website, CAM line etc. (Health Canada, 2013 July; Public Health Agency of Canada, 2008).

Country	Attribute1: Risk Minimization Activities					Attribute 2: Risk Communication Sources				
	A system in place to educate health care professionals on reporting and new adverse reaction issues	Provisions of tracking urgent/general international safety concerns	Regulatory Authorities Requiring Risk Management Plans (RMPs) from NHPs manufacturer	Regulatory Authorities Requiring Summary Reports from NHPs Manufacturers	**Total Attribute Score**	A bulletin or newsletter periodically distributed to HCP	Provisions of website announcements to consumers and HCP	Sending "Dear Health Professional Letters`` in urgent safety issues	Availability of consumer's NHPs information sources	**Total Attribute Score**
Canada	2	2	0	1	**5**	2	2	2	2	**8**
Best Practices Score					**8**	**Best Practices Score**				**8**
Rating Scale	2= Already Exist 1= In development 0= Doesn't Exist			2= Periodic submission 1= Only upon demand 0= not required		2= Frequent (5-6 times/year) 1= less Frequent (2-4) times/year) 0= 1 or less than 1	2= Already Exist 1= In development 0= doesn't Exist			
Periodic submission: The manufacturers are required to submit summary reports to regulatory authorities at specific intervals of time **Only upon demand:** The manufacturers submit summary reports in specific conditions only upon demand by regulatory authorities										

Table 5.1.6: Scores of Canada for "Risk Minimization and Communication"

5.2 Gaps in Canadian Surveillance System in comparison to Best Practices

In this section, gaps between Canadian surveillance system and best practices are assessed. For identifying the gaps, the score of the Canadian surveillance system was compared to the best practice scores per attribute of a dimension as presented in the tables of section 5.1 above. A two step approach was used to highlight the gaps:

1) Recognizing those attributes where Canada's score was less than the best practices scores. If Canada's score is equal to the current best practice, then it was considered that Canada is already doing well for the given attribute.

2) Wherever the Canadian score is less, a further assessment was done to analyse Canadian surveillance system findings against corresponding best practice to identify the gaps. Based on the following description, the results were categorized as follows: No Gap, Minor Gap and Key Gap. These categories help to label the nature of the gaps identified in Canadian surveillance system.

- For a given attribute, if a core or any of the supplementary best practices are completely followed by Canadian surveillance system **= No Gap**
- For a given attribute, if a core and/or any of the supplementary best practice are followed by Canadian surveillance system but not completely = **Minor Gap**
- For a given attribute, if a core and/or none of the supplementary best practices are not at all followed by Canadian surveillance system = **Key Gap**

The following table, Table 5.2 provides details of gaps identified in Canadian surveillance system for each attribute of a dimension in comparison to the best practices:

Dimension	Attribute	Best Practices	Core/ Supplementary	Gaps in Canadian NHP Surveillance System
1.NHPs Post-Market Surveillance System Structure and Stakeholder Coordination	Attribute 2: Coordination and collaborations of stakeholders	Frequent Meetings of Advisory Committee members (5-6 times/year)	Core	**Gap Description**: In Canada, the advisory committees for NHPs meet twice a year face to face to provide NHPD with advice and recommendations on current and emerging NHP issues. **Nature of Gap**: Minor Gap **Importance**: Frequent meetings of advisory committee members address NHPs safety related issues in a continuous and systematic manner; also, provides expert technical advice to the regulatory authorities in a timely manner. These meetings offer a formal platform for experts to address the safety issues of NHPs and co-ordination of surveillance activities (SPS, 2009).
2.Sources of NHPs Adverse Reaction Information	Attribute 2: Other Sources	A system in place to collect NHPs adverse reaction information from National Poison Control Centre (PCC) to identify the signals by regulatory authorities or The Collection of AR reports or information from Herbal medicine practitioner/Organization	Supplementary	**Gap Description:** Currently, Health Canada hasn't established a mechanism to routinely gather or share information from National Poison Control Centres but is conducting some pilot projects to explore the utility of this source. Also, the Canada Vigilance Program accepts reports from all practitioner types, including herbal medicine practitioners, as part of the passive voluntary reporting structure but hasn't developed a system to routinely collect NHPs ARs from herbal medicine practitioner or country's major herbal organisations. **Nature of Gap**: Minor Gap **Importance**: Both of these sources provide unique benefits such as increasing the volume of reports related to herbal/dietary supplements, and gathering useful information in terms of adverse reaction reports through herbal medicine organisation's members (Jordan et al. 2010; Barnes, 2003). These data could increase the ability to detect rare adverse events involving herbal products and can provide wealth of information to regulatory authorities.
2.Reporting of NHPs ARs to Pharmacovigilance Centres	Attribute 1: Reporting Tools	Periodic distribution of Reporting forms to all health care professionals (3-4 times/year)	Core	**Gap Description**: As a regular practice, Health Canada does not distribute AR reporting forms to healthcare professionals **Nature of Gap**: Key Gap **Importance**: The frequent distribution of reporting forms contributes in encouraging HCP to direct report ARs, ensure the wide availability of forms to targeted areas and different groups

Dimension	Attribute	Best Practices	Core/ Supplementary	Gaps in Canadian NHP Surveillance System
				of HCP, and strengthen the reporting systems already in place (Belton, 1997)
3.Data Management and Assessment of Case Reports	Attribute2: Assessment of Case Reports	Provisions of personalized feedback to reporters on association between the drug and reported ARs	Core	**Gap Description**: In Canada, no personalized feedback is given to the reporters on association between the drug and reported AR. The reporters are only acknowledged with the receipt of AR reports **Nature of Gap**: Key Gap **Importance**: The personalized feedback plays an important role in motivating HCP and consumers to report ARs in future, building positive active relationship between reporters and pharmacovigilance center and increasing the understanding and awareness of AR reporting. The newly obtained information from the personal feedback enables more knowledge to become available for use in daily practice (Oosterhuis et al., 2012).
4.Risk Minimization and Communication	Attribute1: Risk Minimization Actions	Regulatory Authorities Requiring Risk Management Plans (RMP) from NHPs manufacturers	Core	**Gap Description**: Canada hasn't implemented any consolidated or standardized procedure for demanding Risk Management Plans (RMPs) from NHPs manufacturers. **Nature of Gap**: Key Gap **Importance**: RMPs from manufacturers contributes in minimizing and preventing risks related to the NHPs. RMPs gives a detailed review of important identified threats of the product, possible risks, and missing information. This information serves as the basis for an action plan for risk management and risk minimization activities (EMA, 2008).
		Regulatory Authorities Requiring periodic submission of summary Reports from NHPs Manufacturers	Core	**Gap Description**: In Canada, NHPs manufacturers prepare summary reports in a PSUR or PBRER format but there is no regulatory requirement on manufacturers to submit these reports. Manufacturers submit these reports only upon demand by Health Canada **Nature of Gap**: Minor Gap **Importance**: The annual summary reports play an important role in providing update information on worldwide safety experience of a product to Competent Authorities at defined time points. "It is an essential source for recognising new safety

Dimension	Attribute	Best Practices	Core/ Supplementary	Gaps in Canadian NHP Surveillance System
				signals, a base of determining changes in the benefit-risk profile, an effective way of risk communication to regulatory authorities and an indicator for the need for risk management initiatives, as well as a tracking mechanism for monitoring the effectiveness of such initiatives"(Health Canada, 2011 November, p.1).

Table 5.2: Identified Gaps in the Canadian NHP surveillance system

The findings of this study demonstrate that most of the NHPs post-market surveillance best practices were already in place and few gaps were identified in Canadian surveillance system in comparison to the best practices. These gaps either minor or key represent an opportunity for Canadian surveillance system to improve and the recommendations provided in the following chapter can be considered to bridge the gaps.

Based on whether a core and/or supplementary best practice(s) completely followed, partially followed or not at all followed, the gaps were categorized into three domains i.e. no gaps, minor gaps and key gaps. As noted in above table (5.2) three minor gaps and three key gaps were identified in the Canadian surveillance system.

Following is a compiled list of both of minor and key gaps:

Minor Gaps

- Frequent Meetings of Advisory Committee members (5-6 times/year)
- A system in place to collect NHPs adverse reaction information from National Poison Control Centre (PCC) or The Collection of AR reports or information from Herbal medicine practitioner/Organization
- Regulatory Authorities Requiring Periodic submission of summary reports from NHPs Manufacturers

Key Gaps

- Periodic distribution of Reporting forms to all health care professionals (3-4 times/year)
- Provisions of personalized feedback to reporters on association between the drug and reported ARs
- Regulatory Authorities Requiring Risk Management Plans (RMP) from NHPs manufacturers

The Table D.1 given in Appendix D represents the list of best practices for those attributes where no gaps were identified in Canadian NHPs surveillance system.

Chapter 6: Recommendations for Canadian NHPs Surveillance System

The previous chapter identifies the gaps between current and future state (best practices) of the Canadian NHPs surveillance system. In this chapter, remedies and possible solutions for tackling or bridging gaps identified in the previous chapter are described. The constructive recommendations provided below are directed at researchers and Health Canada officials so as to make the Canadian NHPs surveillance system more effective.

6.1 Recommendations based on identified Gaps

The following recommendations follow from the gaps identified by dimension of the NHP reference framework.

1) NHPs Post-Market Surveillance System and Stakeholder Coordination

- It is recommended that Health Canada should develop a strategy to increase the interactions among expert advisory committee members. An expert advisory committee plays a major role in reviewing, making policies and technical recommendation on marketed products for their safe use and effectiveness for human use (WHO, 2005). The frequent meetings among committee members can help Health Canada to gain timely advice, recommendations, regular feedback on current/emerging NHPs issues, and facilitate decision making on various NHPs aspects. Also, these meetings provide advisory committee members a podium for sharing specialized skills and discussing necessary developments, for expanding knowledge and checking the efforts are complementary not duplicative and for performing comprehensive mapping of members with defined roles and responsibilities (SPS, 2011; Young, 2012).

2) Sources of NHPs Adverse Reactions Information

- In Canada, the use of Poison Control Center (PCCs) data to increase the number of NHP AR reports and to identify potential safety signal is not utilized. PCCs are recognised as an easily approachable, well-established society resource for consumers and/or healthcare professionals to report adverse events related to NHPs and other medications. It is recommended that Health Canada take initiatives to integrate Poison Control Center (PCC) data with the AR reports obtained through Canadian federal program of reporting i.e. MedEffect™ Canada (Ackroyd-Stolarz et al 2011). The direct reporting of ARs to Health Canada from Canadian poison centres can contribute in increasing the number of ARs reports. Establishment of a mechanism or process to routinely share information from Canadian poison centres will provide Health Canada a

supplementary source of information on NHP adverse reactions. Also, it is suggested that the interested governmental agencies or researchers take initiatives to analyze PCC databases for NHP ARs signals and trends that may warrant formal signal detection methods.

- Health Canada can improve the number of NHPs adverse reaction reports by establishing link and maintaining a regular level of communication with herbal-sector organisations. The current research found that data from these organisations is not widely shared whereas herbal sector organisations could be a valuable source of NHPs adverse reaction information. It is recommended that Health Canada establish contacts and regularly communicate to encourage major NHPs organisations for collecting ARs reports associated with NHPs and herbal medicine treatment from their members. Also, these organizations can be useful in spreading information about NHPs adverse reactions to consumers and introducing a consumer-centred way of gathering complaints and queries regarding marketed NHPs. For encouraging herbal-medicine organisations to collect AR reports from their members, Health Canada can provide incentives in form of issuing certificates or recognition awards on AR reporting. In United Kingdom, MHRA has maintained a link with major organisations of medical herbalist such National Institute of Medical Herbalist (NIMH), Register of Chinese Herbal Medicine (RCHM) etc. to collect NHPs ARs. These organisations request its members to report suspected ARs associated with NHPs, and send an annual summary of ARs report to MHRA. A similar practice can be followed by Canada to collect more number of adverse reaction reports relevant to NHPs.

3) Reporting of NHP ARs to Pharmacovigilance Centres

- Presently, Health Canada is not actively involved in periodic distribution of reporting forms to health care professionals. Many health care professionals mention that unavailability of reporting forms and lack of information on how to report deter them to report adverse reactions (Belton, 1997). Although Health Canada has created MedEffect website for online reporting of ARs but the periodic distribution of reporting forms ensures that these forms are readily accessible to HCPs, and encourages them to directly report ARs (Belton, 1997; Hughes & Wolf, 2008). This step can support in Health Canada's ongoing efforts to enhance the quality and quantity of AR reports, and strengthen the reporting systems already in place. It is recommended that Health Canada distribute reporting forms along with each issue of the Canadian Adverse Reaction Bulletin which is sent three times a year to HCPs. There is often doubt among HCPs on what should be reported, so the back page of Canadian Adverse Reaction Bulletin can attempt to provide directions on reporting and particularly request reports of reactions to newly authorised and suspected NHPs.

4) Data Management and Assessment of Case Reports

- It is recommended that Health Canada provide personalized feedback to the reporters of adverse effects as a valuable step to increase the number of spontaneous AR reports. Many studies showed that respondents like personal feedback instead of a standard acknowledgment letter and this encourages HCPs as well as consumers to report adverse reactions in future. (Palaian, Ibrahim & Mishra, 2011; Oosterhuis, 2012). In New Zealand, the personalized feedback is given to each reporter containing information about the AR from the summary of product characteristics, centre's causality assessment, the number of similar reports in New Zealand and/or the WHO, plus any other additional information such as at-risk groups and prevention issues that may be relevant or topical (Van Hunsel et al., 2012, p. 35). The provision of individual feedback reporters is one of the biggest contributing factors in New Zealand's highest reporting rates per capita as compared to other international spontaneous reporting programmes (Wiktorowicz et al., 2008). Health Canada needs to study the methods that New Zealand uses for providing the feedback to individual reporter and adapt them for the Canadian use.

5) Risk Minimization and Communication

- It is a fact that NHPs produce adverse reactions similar to other therapeutic products and the knowledge on the safety profile of the product is limited at the time of marketing authorisation (EMA, 2007). Health Canada should strengthen their NHPs surveillance system by introducing measures that allow for the early detection, assessment, minimisation and communication of risks related to NHPs in Canada. The Risk Management Plans (RMPs) and annual summary reports for NHPs effectively contribute in minimizing, preventing, communications risks and critical evaluation of the benefit/risk balance of the NHPs. It is recommended that Health Canada set requirements on NHPs manufacturers for submitting summary reports at regular intervals of time and Risk management Plans (RMPs) for any initial market authorisations. Health Canada should consult with NHP manufacturers, NHP expert advisory committee and HCPs to develop strategic plans and standards for implementing RMPs and submitting summary reports at certain intervals of time at least targeting NHPs containing high risk or known adverse reaction ingredients. Also, Health Canada should formally incorporate such plans through legislation and regulations like some European countries.

6.2 Other Recommendations

1. Health Canada can gain improvement in quality of ARs reports by linking Electronic Health Records (EHR) with Canadian adverse drug reaction reporting system. If EHR is interlinked with reporting system, physicians can enter information in real time. Along with that, the drug information system, a component of EHR where physicians can review the complete profile of patient's drug dosage, drug-drug interaction and patient disease history can significantly play important to provide comprehensive information on patients. This information is helpful in ruling out of other possible causes of the AR such as coexistent disease and other medication which may cause ADRs.
2. In Canada, NHPs are widely available from a range of outlets without interacting with healthcare professionals. Health-food stores are major outlets for NHPs and therefore, suspected ARs associated with NHPs may not be identified by healthcare professionals. It is important to encourage public for reporting NHPs adverse reaction and to increase awareness among people regarding misconception for NHPs such as being natural means safe. It is recommended that government should identify new sources for communicating NHPs risks among general public. These sources could be public awareness campaigns displaying posters in health/food stores and health care settings, and through involvement of the mass media and patient/consumer associations, including translation into local languages for the public in general (Skalli & Soulaymani, 2012)

Chapter 7: Conclusion

There is a greater need to monitor and promote the safety and effectiveness of NHPs with the increased access and demand of NHPs in Canada. The post-market surveillance system serves the purpose of developing a national system for tracking and monitoring the adverse reactions of products once they are launched in market (WHO, 2002). Presently, each country has implemented a surveillance system with its unique or similar features and notion of best practices is not clear for the components of NHPs post-market surveillance system. This study applies a comparative analysis approach to recognise the best practices regarding NHPs surveillance system out of different countries' frameworks and identifies what can be learned from these practices for the Canadian surveillance system. To achieve its objectives,, the current research established three research questions and addressed them as follows;

1. What are the best practices for NHPs post-market surveillance and how these practices can be framed based on international applications?

   To answer this research question, a cross-country comparative analysis was conducted against a reference framework. This reference framework was developed as a standard tool for comparative analysis of selected nations using international organisations' guidelines. Each nation's surveillance system was quantified using a scoring scheme and identified best practices based on highly scored countries.
2. What is Health Canada's current framework for post-market surveillance of NHPs and how does this compare with the best practices?

   First, the data were collected on different components of Canadian surveillance system. Next, the findings of Canadian surveillance system was compared with reference framework and measured it in quantitative form similar to other selected nations and lastly compared with best practices to identify the gaps in current Canadian surveillance system.
3. What are the lessons learned from the comparison of best practices and the Canadian post-market surveillance framework toward developing an improved post-market surveillance system for NHPs in Canada?

   To fulfill this research question, recommendations and solutions were provided that can be adopted to fill the key gaps identified in comparison analysis of best practices and Canadian post-market surveillance. These recommendations present constructive ideas that can be adopted by Health Canada and researchers to make Canadian surveillance system more effective.

The results of this study demonstrate that most of the NHPs post-market surveillance activities are already implemented in Canada. However, opportunities exist to advance some components of Canadian NHPs

post-market surveillance framework to the level of identified best practices. The findings from the study revealed that selected nations' NHPs surveillance frameworks ranges from the strong surveillance models of Australia, United Kingdom and Germany to the less rigorous model of Unites States and New Zealand. The Canadian NHPs surveillance system is strong but not as strong as that in Australia and the European countries of Germany and the United Kingdom (UK).

In Canada, efforts are needed to increase the coordination of advisory committee members through frequent meetings, expand the sources of NHPs adverse reaction data through national Poison Control Centres (PCC) and herbal medicine organisations. Special considerations are required for the periodic distribution of reporting forms to healthcare professionals and personalized feedback to reporters for promoting and encouraging different groups to report adverse reactions. Also, careful strategic planning is required to implement compliances requiring Risk Management Plans (RMPs) and periodic submission of summary reports from NHP manufacturers.

By providing best-practices through the experiences and lessons based on international post-market surveillance frameworks, the way is revealed for Canada to develop more rigorous systems for various components of post-market surveillance system such as organisational structure, adverse reaction information sources, data management and assessment, reporting of NHPs adverse reactions and risk management activities that lead to safer and more effective use of NHPs which in turn advance the health of public.

7.1 Limitations

This study has several limitations that as noted in the items presented below.

1) **Data collection through literature review:** The formulation of reference framework and information on Canadian as well as selected countries surveillance framework was collected through literature, document and website review. One intrinsic limitation to literature reviews is the possibility of not capturing all relevant publications. To overcome this issue, several databases were used in this study with the aim of capturing as many published articles relevant to the topic as possible. However there are still chances that many relevant publications may have not been covered.
2) **Reference Framework Indicators**: The study used reference framework indicators to analyse the implementation of various dimensions in selected nations. Through the literature, document, and website reviews there was limited or insufficient information available on implementation of some indicators in selected nations. Thus, those indicators were excluded from the study.

3) **Comparative Analysis:** A second limitation regarding the international frameworks comparative analysis was that it was performed by a single researcher that might cause a bias. Therefore a second researcher analysing the international surveillance system and comparing findings with information presented in the current work can contribute in confirmation of the comparison findings

4) **Lack of Generalization:** These practices were formulated by analysing five countries' surveillance system and may not cover the strengths of other developed nations which were not part of the present comparative analysis study. The formulation of best practices from the broad spectrum of surveillance systems could help in addressing various lapses in NHPs post-market surveillance system. Although the study addressed identified gaps and provided recommendations for strengthening the Canadian post-market surveillance system but this information may not be generalize to every country until and unless there are similarities in basic features of post-market surveillance to the Canadian system. Further studies and reports are needed to indicate specifically individual country's strengths, weaknesses, opportunities, and threats to enable them to develop strategic plans for improvement.

5) **The Scoring Scheme:** The scoring scheme used in current research was developed to score countries responses to the reference framework indicators. The current scoring scheme do not quality the outcome or effectiveness of an indicator implemented in country. Therefore, the use of an elaborated and sophisticated scoring scheme can give a clearer picture on how a given reference framework indicator is implemented in different countries' surveillance framework and how different countries perform in relation to one another.

6) **Case Selection:** In this research, the five countries (Australia, Germany, New Zealand, United Kingdom and United States) were selected as cases on the basis that these are developed nations with well established NHPs Post-market surveillance framework and sufficient information was available on their frameworks. The richness and diversity of these countries in NHPs post market surveillance offers various policy lessons to Canada, yet these countries are required to be comparable on the scale of population size, economic productivity and geographical areas if one require measuring the operationalization or effectiveness of each indicator in a country.

7.2 Future Research Directions

Further research needs to be conducted to do the following:

1) Expand the range of comparator countries by investigating and mapping the characteristics of large number of surveillance systems. This leads to identifying best practice that can be easily generalized to

other nations and there is a potential for their use as a "checklist" to help in assessing other NHPs surveillance systems that are not part of the current study.

2) Explore the additional dimensions and attributes surrounding the NHPs post-market surveillance system such as regulatory agencies' legislation powers and their capacity to enforce changes, decision making process and available resources (financial resources, education and training, staff). These factors would help in knowing the optimal implementation approaches for promoting the NHPs surveillance system in an effective manner.

3) Collect data through personal interviews with representatives of the regulatory authorities. These representatives are directly involved in marketed product surveillance actions and provide detailed insight on current challenges in monitoring NHPs including strengths and weaknesses of a system. Moreover, this data can help in analysing the implementation of additional aspects of a surveillance system, including information that is difficult to collect through a literature review.

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Appendix A: Reference Framework Formulation Guidelines

The following table presents the list of various guidelines used to formulate a reference framework. The table shows the name of guideline document referred, what it is intended to guide and its year of publication.

#	Guidelines	Objectives	Year of publication
1	CIOMS, Current challenges in pharmacovigilance: pragmatic approaches (CIOMS, 2001)	The CIOMS V Working Group has generated proposals for pragmatic approaches to dealing with issues such as classification and handling of individual safety case reports from a variety of sources, approaches to case management and regulatory reporting practice, improvements and efficiencies in the format content and reporting of periodic safety update reports (PSURs) etc.	2001
2	WHO guidelines on good agricultural and collection practices for medicinal plants (WHO, 2003)	Quality assurance of medicinal plant materials used as the source for herbal medicines, and encourage and support the sustainable cultivation and collection of medicinal plants of good quality.	2003
3	ICH Harmonised Tripartite Guideline Post-Approval Safety Data Management: Definitions And Standards For Expedited Reporting E2D (ICH, 2003)	This document provides guidance on definitions and standards for post-approval expedited reporting, as well as good case management practices with consideration as to how the terms and definitions can be applied in the post-approval phase of the product life cycle.	2003
4	WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance system (WHO, 2004)	Provide technical guidance on the principles of good pharmacovigilance practices for herbal medicines in existing national drug safety monitoring systems	2004
5	ICH Harmonised Tripartite Guideline Pharmacovigilance Planning E2E (ICH, 2004)	This report summarises the methodologies available to industry and regulations in conducting good pharmacovigilance; provides methods particular for data collection through active and passive surveillance.	2004
6	National policy on TM and regulation of herbal medicines Report of a WHO global survey (WHO, 2005)	Main objectives of this report are framing policy for safety, efficacy, and quality of herbal medicines and its promoting rational use.	2005
7	VOLUME 9 The Rules Governing Medicinal Products in the	This report brings together general guidance on the requirements, procedures, roles and activities in this field, for both Marketing Authorisation Holders and Competent	2008

	European Union– Guidelines on Pharmacovigilance for Medicinal Products for Human Use (EMA, 2008).	Authorities of medicinal products for human use; it incorporates international agreements reached within the framework of the International Conference on Harmonisation (ICH).	
8	Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries (SPC, 2009)	This report provides a comprehensive description and analysis of national pharmacovigilance systems in sub-Saharan African (SSA) countries by using an indicator-based performance monitoring tool for assessing pharmacovigilance and medicne safety systems. This document informs development and implementation of a improved pharmacovigilance model.	2009
9	European Medicine Agency, Guideline on good pharmacovigilance practices: Module VI – Management and reporting of adverse reactions to medicinal products (EMA, 2012).	This Module addresses the requirements applicable to competent authorities marketing authorisation holders and the Agency as regards the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the European Union (EU).	2012
10	European Medicine Agency, Guideline on good , Guideline on good pharmacovigilance practices (GVP), Module XV – Safety communication (EMA, 2013).	This Module provides guidance to marketing authorisation holders, competent authorities in Member States and the European Medicines Agency on how to communicate and coordinate safety information in the EU	2013

Table A.1: Guidelines Used for Reference Framework with their Objectives and Year of Establishment

Appendix B: NHPs Post-market Surveillance Reference Framework

This Appendix presents the reference framework consisting of the characteristics which are important for the usefulness and effectiveness of NHPs Post-market surveillance practices. The review of international organisations guidelines and published articles resulted in six broad characteristics called dimensions which were further categorised into attributes and indicators. These dimensions, attributes and indicators form of a complete reference NHPs post-market surveillance system. The following are the six major dimensions of NHPs post-market surveillance framework identified in this study:

1. NHPs post-market surveillance system structure and stakeholder coordination
2. Laws and Regulations for NHPs
3. Data collection on NHPs adverse reactions
4. Reporting of Adverse drug reactions
5. Data Management and Assessment of Case Reports
6. Risk Minimization and Communication

The following is a brief explanation of each dimension along with its attribute and indicators:

1. NHPs post-market surveillance System Structure and Stakeholder Coordination

The development of sustainable structures and their optimal functioning are critical to NHPs post-market surveillance system. The lack of well integrated pharmacovigilance activities and coordination into regulatory functions and structures can lead to insufficient performance. The countries should strengthen organizational structures for pharmacovigilance at all levels of the health system and coordinate activities among all stakeholders. This dimension was categorised into two attributes, as explained below:

1.1 Structure Elements: The elements that shape the functioning of a post-market surveillance system. The structural elements determine the mode in which an organization operates and performs to achieve organisational aims. It consist of various enteritis such as departments, workgroups or individuals with specific functions and processes.

1.2 Coordination and Collaboration of Stakeholders: Post-market surveillance system involves multiple stakeholders such as regulatory authorities, WHO, advisory committees and other national monitoring centres. Proper coordination is required to ensure that no gaps exist and that communication and opportunities for leveraging resources are exploited (SPS, 2009).

Following are the indicators for each attribute of NHPs post-market surveillance system structure and stakeholder coordination:

Attribute	Indicators
1.1 Structure Elements	**1.1.1 Presence of a regulatory agency or relevant department for NHPs**: A regulatory agency is defined as the programme performed on local or national level, by the ministry of health, by other ministries, or by local bodies, whose mandate is to take concrete action in order to achieve objectives in line with the national policy or legislation (WHO, 2005).
	1.1.2 A National Pharmacovigilance Centre covering NHPs in their scope: Pharmacovigilance units should include herbal medicines in the current scope of their activities (WHO, 2004; SPS, 2009)
	1.1.3 Existence of a Expert Advisory committee on safety of NHPs: The multi-disciplinary advisory committee is desirable to provide advice and performing safety evaluations of NHPs (WHO, 2004; WHO, 2005).
	1.1.4 A national research Institute for NHPs: A national research institute for NHPs or herbal medicines performs research on NHPs and provide scientific evidence for the efficacy and safety of herbal products. (WHO, 2005).
1.2 Coordination and collaboration of stakeholders	**1.2.1 Frequent Meetings of advisory committee:** An advisory committee should meet frequently and provides advice on medicine or NHPs safety to the national regulatory agency and the Pharmacovigilance centre. These meetings provide a formal platform for experts to address the safety issues of NHPs and co-ordination of surveillance activities (SPS, 2009).
	1.2.2 Collaboration with WHO and Other National Monitoring Centres: The regulatory Agency and the international (WHO/UMC Centre) and other national monitoring centres (e.EMA, FDA) should exchange information. Sharing of information ensures that new safety alerts are shared and acted on in a timely and coordinated manner (SPS, 2009; WHO, 2004).

Table B.1: Reference framework for dimension "NHPs post-market surveillance System Structure and Stakeholder Coordination"

2. Laws and Regulations for NHPs

Laws and regulations are necessary to provide legal backing for Post-market surveillance and NHPs safety activities. Regulations are derived from the legislation to guide the implementation of the law. A law is the first stage of legislative procedures; establishes the legal conditions under which NHPs should be organized in line with a national NHPs policy where as the regulations are the second stage of legislative procedure, specifically designed to achieve the commitments and goals of a law (WHO, 2005).

This dimension was categorised into two attributes:

2.1 The Laws for NHPs: A law is the Initial stage of governmental procedures; it is a rule of conduct imposed by the authority. A law establishes the legal conditions under which NHPs should be organized. The law could cover different areas in the NHPs field such as licensing of NHPs and

manufacturers, sales practice etc .(WHO, 2005).The laws that govern the sale of herbal products to the general public. The legal definition that is assigned to herbal products determines their classification and the manner in which their sale and use is controlled. It is important to induce the status of herbal products according to their therapeutic claims, achieve harmonization within the market and safety of public (Forte and Raman, 2000).

2.2 Regulations for NHPs Manufacturers/ Licensers: National drug regulatory authorities require establishing guidelines on herbal medicines licensing process. These measures are vital for ensuring the safety, quality and efficacy of herbal medicines. Weak regulation and quality control may result in a high incidence of adverse reactions attributable to poor quality of herbal medicines, in particular resulting from adulteration with undeclared potent substances (WHO, 2003; WHO; 2005).

Attribute	Indicators
2.1 Law and Legislation for NHPs	**2.1.1 A National Legislation for Regulations of NHPs**: In a country, there should be a national law on NHPs which can govern legislative procedures for licensing, sale, manufacturing and exporting/importing for NHPs (WHO, 2005; Forte and Raman, 2000).
	2.1.2 The licensing or Registration System for NHPs: The NHPs require to be licensed before they can be put on the market based on review of evidence and risk evaluations. In most of the countries, NHPs are licensed based upon the claims they made. The first one is medicinal claims having intention to treat or prevent disease correct or modifies physiological function and second is non-medicinal claims used to supplement the diet or to maintain/promote the health (WHO, 2005; Harrison, 2008).
	2.1.3 The law on control of NHPs advertisements: The national authorities responsible for the regulation of herbal medicinal products should approve every advertisement before it reaches the public. The regulatory authority should issue advertisement permits after satisfactory evaluation of the contents of each advertisement to ensure that the public gets the correct information about the product, devoid of ambiguous or fraudulent claims. The print and electronic media should be notified to ensure that every advertiser of herbal medicinal products obtains the permit from the national authority before such an advertisement is published (WHO, 2003).
	2.1.4 The legal status given to NHPs for sale in market based upon their medicinal/non-medicinal claims: Based upon medicinal and non-medicinal claims of NHPs, there should be restriction on the sale of these products in the market. The NHPs having medicinal value should be sell in the supervision of pharmacist with prescriptions only (WHO, 2005; Forte and Raman,2000).

2.2 Regulations for NHPs licensers	**2.2.1 Requirements on Providing evidences of quality, safety and efficacy for for NHPs**: All NHPs should meet the requirements for safety, efficacy and Quality and regulators should ensure that the product is safe under the recommended conditions of use, effective for the proposed claims, and of high quality. The countries require that manufacturers wishing to obtain registration for their NHPs under a national scheme should demonstrate the quality, safety and efficacy of their products (WHO; 2003, WHO, 2004; WHO, 2005; Jordan et al.2011).
	2.2.2 The obligations on manufacturers to adhere to GMP practices : The GMP practices ensures the systematic quality control throughout the manufacturing process. The basic requirements of GMP include areas such as quality management, personnel, premises and equipment, documentation, production, quality control, contract manufacture and analysis, complaints and product recall and self inspection. It is important for manufacturers to adhere to GMP practices set by regulatory authorities for the appropriate quality of NHPs (WHO; 2003, WHO, 2004; WHO, 2005).
	2.2.3 Labelling specifications for manufacturers: Manufacturers of products registered under the directive required to comply with information and labelling requirements (Forte and Raman, 2000; WHO; 2003)

Table B.2: Reference framework for dimension "Laws and Regulations for NHPs"

3. Sources of NHPs Adverse Reaction Reports Information

The term data collection refers to the variety of ADRs information sources which contribute the understanding and finding a causal relationship between drug and disease. Competent authorities and marketing authorisation holders should take appropriate measures in order to collect and collate all reports of suspected adverse reactions associated with NHPs (SPS, 2009). This dimension was categorised into two attributes:

3.1 Surveillance Approaches: The most common way of collecting information on adverse reaction is through active and passive surveillance. The passive surveillance includes spontaneous adverse reaction reporting system in which reports are collected from healthcare professionals, consumers and manufacturers whereas active surveillance include the pre-organised procedures to collect AR reports

3.2 Other Sources: There are multiple sources from where data can be collected on NHPs adverse reactions. The agencies should be well prepared for collecting routine data coming from different source. The following is a brief description of indicators indentified for each attribute.

Attribute	Indicators
3.1 Surveillance Approaches	**3.1.1 Existence of Passive surveillance system for NHPs:** A passive surveillance is called as spontaneous reporting which is unsolicited communication by healthcare professionals, consumers and manufacturers to the regulatory authority or organisations (ICH, 2004).
	3.1.2 Implementation of Active surveillance system for NHPs: It seeks to ascertain completely the number of ADR via a pre-organised process. Active surveillance includes a wide range of approaches such as registries, sentinel sites, prescription event monitoring etc. (ICH , 2004; CIOMS, 2001).
3.2 Other sources	**3.2.1 A system in place to collect NHPs adverse reaction information from National Poison control centre (PCC):** Problems and adverse reaction information associated with herbal medicines can be collected from Poison control centre. PCC data could increase the ability to detect rare adverse events involving herbal products by combining its data with national databases to increase the ability to detect rare adverse events involving herbal products (WHO, 2004; Jordan, Cunningham and Marles,2010)
	3.2.2 The foreign Adverse Reaction Reports: In most of the nations, it is the legal responsibility of manufacturers to submit all reports of suspected unexpected adverse reactions that are serious and that occurred in a third country where they hold a marketing authorisation (ICH, 2004; EMA, 2012; CIOMS, 2001).
	3.2.3 Published literature: The scientific and medical literature is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. It is important for regulators to ask from its manufactures to be aware of cases from worldwide literature and inform regulatory authorities (CIOMS,2001; ICH, 2004; EMA ,2012).
	3.2.4 Information on suspected adverse drug reactions from the internet or digital media: National agencies require from its manufactures to regularly screen websites for potential ADR case reports. It is also recommended that the marketing authorisation holder actively monitor special internet sites or digital media in order to check if they describe significant safety issues which may necessitate reporting (ICH, 2003; EMA, 2012).
	3.2.5 Information from World Health Organization (WHO) database: The National agencies should participate in WHO pharmacovigilance monitoring program. WHO Receives and store the reports from national pharmacovigilance centre. It provides the provision of facilities to enable national pharmacovigilance centres to search the global WHO database and generation of signals from the global WHO database (WHO, 2003).
	3.2.6 A system in place to collect NHPs AR reports from Herbal medicine practitioner/Organization: The Herbal medicine organisation can provide a wealth of information on NHPs adverse reactions. National regulatory agencies should established a good level of communication with such centres. The herbal medicine organisations can collect AR reports from its members regarding any type of NHPs

	in the marketplace and may obtain relevant information about herbal medicines (Barens, 2001).

Table B.3: Reference framework for dimension "Sources of NHPs Adverse Reaction Information"

4. Reporting of Adverse drug reactions to Pharmacovigilance Centre

Adverse reaction reporting provides a system to collect ADR data and allows the regulators to implement measures to protect the public (Harrison, 2008). Manufacturers, professionals, and consumers report adverse reactions to regulatory authorities using a reporting form which is stored in database and assessed to find the important relationship between drug and disease. It is categorised into two attributes:

4.1 Reporting Tools: The various tools are required to implement in a country for facilitating consumers, healthcare professionals and manufactures to submit reporting forms to national/regional pharmacovigilance centres regarding any complaint of marketed products.

4.2 Reporting Requirements: Reporting requirements are either volunteer or mandatory set by authorities to ensure public privacy, security and safety.

Attribute	Indicators
4.1 Reporting Tools	**4.1.1 The existence of facility of Reporting via Telephone, email, Fax and post to consumers and Healthcare Professionals:** It is desirable to accept ADR reports through telephone, email, fax and post.
	4.1.2 The Provisions of Electronic /Online Reporting to consumers and Healthcare Professionals: This reporting tool facilitates the reporting of adverse drug reactions to the pharmacovigilance centre and uses an online reporting form pre-populated with patient details. According to CIOMS (2001), the emerging tools and technology such as electronic reporting shows great promise for efficiencies in data management and communication. These forms are mostly based on an International Conference on Harmonisation standard (ICH) for exchanging information (Van Hunsel et. al., 2012).
	4.1.3 Periodic Distribution of Reporting Forms to all healthcare professionals: The reporting forms should be distributed to healthcare professionals on periodic basis with the guidelines on how to report adverse reactions (WHO, 2004).
	4.1.4 Distribution of Reporting form to herbalist/herbal medicine practitioner: Consideration should be given to the distribution of reporting forms to those involved in the provision of herbal medicines, such as providers of traditional medicine and complementary/alternative medicine, who may not previously have been part of the national pharmacovigilance system (WHO, 2004).

	4.1.5 Modifications in National AR reporting form to cover NHPs: WHO (2004) recommends that, a single reporting form covering all medicines, including herbal medicines, should be used. **T**he reporting form for herbal medicines could be the same as that used for other medicines but modifications should be done to their national reporting forms to facilitate the reporting of suspect reactions to herbal medicines, interactions between herbal medicines and other medicines (WHO, 2004; Barnes, 2003).
	4.1.6 Separate section for NHPs: By adding a separate small section on NHPs in national reporting form, the important detail on herbal medicines can be requested such as listing ingredients, labels or name/address of manufactures/distributers which are helpful to identify the complex ingredients of herbal medicines producing ADR (Barnes, 2003).
4.2 Reporting Requirements	**4.2.1 Including Health Care Professionals as volunteer reporters by national reporting scheme:** To strengthen pharmacovigilance activity in the non-prescription medicines setting, It is important to encourage volunteer reporting by community pharmacists ,nurses, dentist, midwives and other healthcare professionals along with physicians (WHO, 2004; WHO, 2005; SPS, 2011)
	4.2.2 Including Consumers as volunteer reporters by national reporting scheme: For NHPs, often taken without health professional involvement, reports received directly from consumers may provide the source of signals. Patients/consumers should report on volunteer basis to physicians or directly to pharmacovigilance centres. "However, only a few national regulatory authorities currently explicitly require collection of direct reports from consumers. The CIOMS Working Group proposes several policy approaches and practices aimed at ensuring that consumer reports are treated with appropriate respect and that there is a rational approach for handling them (Annex 4)" (WHO, 2004).
	4.2.4 The requirements on manufacturers to report NHPs adverse reaction to regulatory authorities: Manufacturers of NHPs are the important source of information on adverse events associated with their products. In most of the countries, manufacturers are obliged to report NHPs adverse reaction as part of the regulatory framework (WHO, 2004; CIOMS, 2001).

Table B.4: Reference framework for dimension "Reporting of Adverse drug reactions to Pharmacovigilance Centre

5. Data Management and Assessment of Case Reports

The increasing volume of data produced during post-market surveillance of medicinal products has produced a need for specialised procedures, technologies and standards to manage, analyse and interpret pharmacovigilance data. The dimension leads to two attributes named as

5.1 Data Management: This attribute highlights the requirement of database and technology to exchange information between different stakeholders in ways which ensure the quality and

integrity of the data collected. Accurate, complete, and bona fide information is very important for MAHs and regulatory agencies for identifying and assessing ADR reports (ICH, 2003)**.**

5.2 Assessment of Case Reports. The assessment of adverse reaction case reports include evaluation of reports using causal categories and signal detection methods. Also, it requires combined expertise in clinical medicine, pharmacology, toxicology, and epidemiology (CIOMS, 2010; WHO, 2000). The following is the dimension-attribute and indicator framework for Data Management and Assessment of Case Reports.

Attribute	Indicators
5.1 Data Management	**5.1.1 Coding of NHPs Adverse Reactions using MedDRA**: The Coding of adverse events/adverse reactions to herbal medicines should be compatible with that for other medicines. The Coding of NHPs ADR should be performed using the latest version of the ICH-Endorsed Medical Dictionary for Drug Regulatory Activities (MedDRA) (WHO, 2004; EMA, 2012)
	5.1.2 Availability of technology for the electronic exchange of Information between MAH and regulatory authorities according to ICH standards: To minimise preparation time, costs of processing submitted data, uniformity and a high quality of submission content it is beneficial to implement technologies for the rapid transmission of pharmacovigilance information between multiple stakeholders. This indicator highlights the requirements for the establishment of data processing network in order to collate and share pharmacovigilance information electronically between competent authorities, marketing authorisation holders and the Agency, in ways which ensure the quality and integrity of the data collected. The information provided here is relevant for the electronic exchange of ICSRs between all stakeholders. The guidelines ICH-E2B provides the detail guidelines on standards for preparing reports in electronic format to facilitate direct database-to-database transmission (ICH, 2003; EMA, 2008).
	5.1.2 Mechanism to check quality of ADR reports (integrity, completeness and duplicates): A procedure should be in place to account for completeness, quality, integrity and duplications of ADR reports. It is important to make sure that there are quality controls on data processing and that the data elements of reports are as complete and accurate as possible. Mechanisms to check for duplications should be instituted (WHO, 2004, EMA, 2012, CIOMS, 2001). Patient and reporter identifiability is important to avoid case duplication, detect fraud, and facilitate follow-up of appropriate cases (ICH, 2003). The certain characteristics of a case (sex, age or date of birth, dates of drug exposure, etc.) may be used to identify duplicate reporting (WHO, 2000).
	5.1.5 A system to conduct Follow-up actions: When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary, to obtain supplementary detailed information relevant for the scientific evaluation of the cases.

	5.1.6 A national legislation on keeping confidentiality and Security of patient's information: Confidentiality of Patients' records including personal identifiers, if provided, should always be maintained. Identifiable personal details of reporting Healthcare Professionals should be kept in confidence, as appropriate and in keeping with national legislation (WHO, 2004; EMA, 2012).
5.2 Assessment of Case Reports	**5.2.1 Use of WHO causality categories for assessing case reports**:. The causality assessment can be defined as a method of finding the relationship between the intake of a medicine and an adverse reaction. According to WHO (2004), "assessment of reports on adverse reactions to herbal medicines should be undertaken by national pharmacovigilance centres in the same way as for other medicines". WHO proposed technique for causality assessment called "causality categories" which benefit from long and extensive use and have the advantage of being internationally agreed and easy to use. (WHO_2004).
	5.2.2 Use of Signal Detection Techniques: According to CIOMS (2010), a signal can be defined as information that arises from one or multiple sources which advise a new, potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action". Signal detection doesn't specify the causal relationship between drug and a reported adverse reaction but trigger the need for further investigation to confirm a potential association. This task is done by using various Signal detection techniques such as calculation of the proportional reporting ratio (PRR), Bayesian methods etc. (ICH, 2003).
	5.2.3 Provisions of Personalized feedback to reporters: The personalized feedback is further information than just acknowledgment. The feedback consist of receiving additional information about the reaction concerned such as the number of similar reports in a country and/or WHO, plus any other information about the reported association. Such feedback will motivate the reporter to send in further reports (WHO, 2004; Van Hunsel et al. 2012).
	5.2.3 Acknowledgement given to the reporters on receipt of each report: Acknowledgement is a quick confirmation of the receipt of the report. According to WHO (2004), a new reporting form should be supplied to the reporter as well as links to the electronic monthly bulletin or Drug Safety Updates with the receipt of each report (WHO, 2004; Van Hunsel et al. 2012).
	5.2.4 The assessment of reports done in cooperation with an expert panel comprising experts in multidisciplinary areas : The assessment should be done in cooperation with an expert panel comprising experts in pharmacognosy, toxicology and other health professionals including providers of herbal medicines (WHO, 2004)

Table B.5: Reference framework for dimension "Data Management and Assessment of Case Reports"

6. Risk Minimization and Communication

Risk is mitigated through accurate and timely communication of risk to different stakeholders, organized arrangement of quality assurance and taking appropriate actions after identifying a risk**.**

This dimension is categorised to two attributes

6.1 Risk Minimization Activities: This attribute refers to methods or tools used for preventing and minimizing risks that could occur after post-authorization of health products. it includes spreading awareness among consumers and health professionals regaining NHPs ADR, a systematic method to track foreign regulatory actions, formal risk management activities and requiring periodic summary reports from manufacturers.

6.2 Risk Communication Tools: The risk communication deals with the process of exchanging risk information with stakeholders such as healthcare professionals, consumers, manufacturers etc. It includes disseminating monthly newsletter or bulletin detailing updated safety issues, website announcements, Dear Health Professional letters, availability of consumer information sources where they can avail current information on NHPs.

Attribute	Indicators
6.1 Risk Minimization Activities	**6.1.1 A system in place to educate health care professionals on reporting and new adverse reaction issues**: Education in the appropriate use of herbal medicines, reporting personal adverse experiences to healthcare providers is essential for patients and health-care providers. Companies and regulators should convey this message through educational materials or in the course of responding to consumer inquiries or complaints (WHO, 2000; WHO, 2004; EMA, 2013).
	6.1.2 Provisions of tracking urgent/general international safety concerns: During the marketing period of health product, urgent measures to safeguard public health may be necessary. A strategy to manage and minimize risk is to exchange information regarding safety concerns, particularly those which may result in major changes to the marketing authorisation status or revocation or withdrawal of a product, between the local and international pharmacovigilance agencies. An example of such kind of system to share urgency safety matters is European rapid alert information system (EMA, 2013). Medicine safety issues of local relevance identified from outside sources can be used to prevent any possible harm in the local population. Those sources of information that countries can easily access and use to inform locally relevant decisions are safety newsletters from WHO, publications such as Reaction Weekly, and safety alerts from FDA and EMA (SPS, 2011; SPS, 2009)
	6.1.3 Requiring Risk management plans (RMPs) from NHPs manufacturers: In most of the countries, competent authorities require RMPs as part of a product's approval process or for an approved product when new safety information emerges (SPS , 2009; EMA, 2005). The RMPs give a comprehensive review of what is known about the safety of the product, what important information about safety is currently missing, manufacture's proposal to resolve the gaps and how the company proposes to reduce the severity or frequency of known adverse reactions.

Attribute	Indicators
	6.1.4 Regulatory Authorities Requiring Summary Reports from NHPs manufacturers: The summary reports are intended to provide an update of the worldwide safety experience of a product to Competent Authorities at defined time points post-authorisation. It includes all ARs reported in the period since the last summary report, together with a review of the registration status of the product worldwide, actions taken for safety reasons, the worldwide usage of the product and an analysis of safety product The Periodic safety Update Reports (PSURs), Annual Summary Reports (ASR), Periodic Benefit Risk Evaluation Report (PBRER) are recommended formats by ICH standards. Most of the countries require these summary reports in specific formats (PSURs, ASR, PBRER) from their manufacturers at different set of intervals of time (EMA, 2008; CIOMS, 2001; ICH, 2003).
6.2 Risk communication sources	**6.2.1 A bulletin or newsletter periodically distributed to all healthcare Professionals:** ADR or medicine information bulletins and newsletters distributed at regular interval of times are key communication tool for informing health care providers and consumers about significant medicine safety issues (WHO, 2004; EMA, 2013)
	6.2.2 Provisions of website announcements to consumers and HCP regarding product withdraw, Recalls, and safety warnings: Competent authorities as well as marketing authorisation holders should ensure that important safety information published on websites under their control in easily accessible and understandable manner by public.
	6.2.3 Sending "Dear Health Professional Letters`` in urgent safety issues: When new medicine safety issues arise either from spontaneous reports or from global safety literature scanning, relevant information and alert letters should immediately be sent to health care professionals to alert them of the safety concerns (SPS, 2009; EMA, 2008).
	6.2.4 Availability of Consumer Information sources: Consumers need easily accessible information about NHPs. This information should be reliable, objective and, where possible, based on sound evidence. High-quality consumer information about NHPs is necessary to ensure public safety and to enable people to make informed choices about their health care.

Table B.6: Reference framework for dimension "Risk Minimization and Communication"

Appendix C: The Comparative Analysis of Selected Countries with Reference Framework

This Appendix consist of tables C1 to C6 presenting a summary view of comparative analysis of selected nations and reference framework. These tables gives information on how each country implemented the indicators of each attribute of a dimension.

Reference Framework			International Frameworks				
Dimension	**Attributes**	**Indicators**	**Australia**	**Germany**	**New Zealand**	**United Kingdom**	**United States**
1. NHPs Post-market Surveillance Structure and Stakeholder Coordination	1.1Structure Elements	1.1.1Presence of regulatory agency for NHPs	Therapeutic Goods Administration (TGA)	The Federal Institute for Drugs and Medical Devices (BfArM)	New Zealand Medicines and Medical Devices Safety Authority (Medsafe)	Medicine and Healthcare Products Regulatory Agency (MHRA)	The United States Food and Drug Administration (FDA)
		1.1.2 National Pharmacovigilance Centre including NHPs in their scope	Yes	Yes	Yes	Yes	Yes
		1.1.3 Expert group on safety of NHPs	Yes; The Expert Committee on Complementary Medicine (ECCM)	Yes, Commission E	Yes, Advisory Committee on Complementary and Alternative Health (MACCAH)	Yes, Herbal Medicines Advisory Committee (HMAC)	Yes, The Dietary Supplements Information Expert Committee (DSI-EC)
		1.1.4 A national research Institute for NHPs	Yes; many	No	No	Yes; many	Yes; many
	1.2 Coordination and collaboration with stakeholders	1.2.1 Frequent Meetings of advisory committee	Yes; 6-8 times/year	Yes, 3 times/year	Yes; 4 times/year	Yes, 6 times/year	Yes; 4times/year
		1.2.2 Collaboration with WHO and Other National Monitoring Centres	Yes; collaborated with WHO, New Zealand, Singapore, Japan and USA	Yes; WHO , EMEA and other European countries	Yes; shares safety information with WHO, FDA, TGA and EMEA	Yes; collaborated with WHO, ICH, EMEA and European countries	Yes, collaborated with WHO, TGA,EMEA

Table C.1: A comparative analysis for selected countries on "NHPs Post-market Surveillance Structure and Stakeholder Coordination"

Reference Framework			International Frameworks				
Dimension	**Attributes**	**Indicators**	**Australia**	**Germany**	**New Zealand**	**United Kingdom**	**United States**
2. NHPs Laws and Regulations	2.1 The Law and Legislation on NHPs	2.1.1 The existence of national law on regulations of NHPs	Yes, a national law on NHPs was implemented as Therapeutic Goods Act (TGA) issued in 1989	Yes; ArzneiMittel Gezetz (AMGO issued in 1976	Yes; NHPs are regulated under the Medicines Act of 1981 and under the Dietary Supplements Act of 1985	Yes; The Medicine Act 1968 and Food safety act 1990.	Yes, Dietary Supplement Health and Education Act of 1994
		2.1.2 The licensing or Registration system for NHPs before selling into the market	Yes; The NHPs require license before sale into the market. The licensing process for registered Medicines (RG)is more detailed than listed Medicines (LM)	Yes;	No	No	No; Dietary supplements do not require license before they are marketed.
		2.1.3 The legal status given to NHPs for sale in the market based upon risk evaluations	Yes; The products which are evaluated as low risk called listed (LM) and high risk as Registered Medicines (RM). the RM are sold as prescription and LM as over-the-counter	No	Yes; NHPs are regulated as dietary supplements and medicines	Yes; licensed and unlicensed herbal medicines	NHPs are regulated as Dietary supplements and drugs (NHPs claiming medicinal values)
		2.1.4 Law on control of NHPs advertisements	Yes; advertisements to the general public for herbal products (listed and registered) must be pre-approved	Yes, compliance with advertise requirements is ensured through inspections	Yes, manufacturers are required to comply with advertisement regulations	Yes, for licensed and unlicensed products	Yes, FDA can charge manufacturers in case of violation of advertisement regulation
	2.2. Regulations for NHPs Manufacturers	2.2.1 Requirement on providing evidences of quality and efficacy from MAH	Yes; but only for registered NHPs	Yes; Commission E approves NHPs based on product quality, safety and efficacy	NO; for NHPs regulated as dietary supplements	Yes; for licensed herbal medicines	NO: for NHPs regulated as dietary supplements
		2.2.2 Requirement on providing evidences of safety of NHPs from MAH	Yes	Yes; for all products	NO	Yes; for licensed products	Yes; manufacturers are responsible for ensuring that DS is safe before it is marketed.
		2.2.3 Obligation on adherence to GMP practices by	Yes; NHPs manufacturers require to comply with the Australian code of GMPs	Yes; the same rules apply as conventional	No; GMP rules apply voluntarily for dietary supplements	Yes; GMP rules are require for licensed herbal medicines	Yes, FDA maintains quality standards by strict

Reference Framework			International Frameworks				
Dimension	**Attributes**	**Indicators**	**Australia**	**Germany**	**New Zealand**	**United Kingdom**	**United States**
		manufacturers		medicins			control on GMP practices for dietary supplements
		2.2.4 Labelling specifications for manufacturers	Yes	Yes	Yes, specific labeling requirements for dietary supplements	Yes, labelling requirements are applicable to all herbal medicinal products	Yes, FDA set strong requirements for labelling of dietary supplements

Table C.2: A comparative analysis of selected countries on "NHPs Laws and Regulations"

Reference Framework			International Frameworks				
Dimension	**Attribute**	**Indicators**	**Australia**	**Germany**	**New Zealand**	**United Kingdom**	**United States**
3.Sources of NHPs Adverse Reactions Reports	3.1Surveillance approaches	3.1.1 Passive surveillance	Yes; through blue card spontaneous reporting scheme	Yes	Yes; through Centre for Adverse Reactions Monitoring (CARM) programme	Yes; A yellow card scheme is used for spontaneous reporting	Yes
		3.1.2 Active surveillance	No, only for medicinal products	Yes; through registries, patient use programs, patient support and disease management programs etc.	No, only for medicinal products	No; there is no active surveillance for NHPs, only for medicinal products	No, only for medicinal products
	3.2 Other sources	3.2.1 Use of Data from National Poison control centre (PCC)	No	No	No	No	Yes, FDA collects ADR data on dietary supplements from PCC
		3.2.2 Foreign adverse reaction reports	Yes, through manufactures	Yes; manufactures are expected to perform these duties	Yes	Yes; manufacturers are liable to notify any significant safety issues through foreign adverse reaction reports	No; FDA ask its manufacturers to inform voluntarily regarding foreign ADR information
		3.2.3 Literature scan	Yes	Yes, from world-wide literature	Yes; manufactures are expected to conduct literature review of widely used reference databases and aware of publications in the local journals	Yes	Yes
		3.2.4 Internet or digital media	Yes	No; BfArM does not expect the manufacturers screen the internet regularly for ADR associated with the use of their products.	Yes	Yes, manufacturers are expected to regular screening of internet or digital media	Yes

Reference Framework			International Frameworks				
Dimension	**Attribute**	**Indicators**	**Australia**	**Germany**	**New Zealand**	**United Kingdom**	**United States**
		3.2.5 Information from World Health Organization (WHO) Database	Yes; member of the WHO pharmacovigilance network and has access to the WHO international database	Yes; BfArm is active member of WHO monitoring program and have full access to WHO database	Yes; being an active member to WHO international monitoring program has full access to its database	Yes	Yes
		3.2.6 ADR reports from Herbal medicine practitioner/Organization	No	No	No	Yes; through various herbal sector own reporting schemes	No

Table C.3: Comparative analysis of selected countries for "Sources of NHPs Adverse Reactions Reports"

Reference Framework			International Frameworks				
Dimension	**Attribute**	**Indicators**	**Australia**	**Germany**	**New Zealand**	**United Kingdom**	**United States**
4.Reporting of NHPs Adverse Reactions to Pharmacovigilance Centre	4.1 Reporting Tools	4.1.1 Reporting via Telephone, email, Fax, post	Yes	Yes	Yes	Yes	Yes
		4.1.2 Electronic /online Reporting	Yes; an electronic form is available on TGA website	Yes	Yes; electronic forms are able to automatically capture patient details from General practiotire's software	Yes;, the electronic forms are more sophisticated and allow checks for completeness and importation of data directly to a database	Yes; through MedWatch website
		4.1.3 Distribution of Reporting Forms to health care professionals (HCP)	Yes; blue cards are distributed to HCP four times / year	No, reporting form are available on BfArM website and can be downloaded	No	Yes; twice/year	No
		4.1.4 Distribution of reporting forms to herbalist/ herbal organisations	No	No	No	No	No
		4.1.5 National ADR reporting form covering NHPs	Yes; the same reporting form used for conventional medicines ask reporter to report ADRs related to NHPs	Yes	Yes; ask reporters to report ADRs related to NHPs and other alternative medicines	Yes	Yes; a section to report ADRs including dietary supplements and any ask reporters to report if they take any concomitant medicines including dietary supplement
		4.1.6 A Separate section for NHPs in national reporting form	No	No	No	No	No

Reference Framework			International Frameworks				
Dimension	**Attribute**	**Indicators**	**Australia**	**Germany**	**New Zealand**	**United Kingdom**	**United States**
	4.2 Reporting Requirements	4.2.1 Volunteer reporting by Health Care Professionals	Yes	Yes; All HCP sent ADR reports based on self commitment under the physician's code of conduct	Yes	Yes	Yes
		4.2.2 Volunteer reporting by consumers	Yes	No; BfArM accepts reports of adverse effects only from health professionals since the scientific assessment of reported events requires specialised medical information	Yes	Yes	yes
		4.2.3 Obligatory reporting by manufacturers	Yes; in an expedited manner if serious reaction occurs.	Yes; in an expedite manner	Yes	Yes; impose obligations to report any serious and unexpected ADR within 15 days (expedite manner)	No; FDA doesn't impose any legal obligation on manufacturers to report ADRs associate with NHPs.

Table C.4: Comparative analysis of selected countries for "Reporting of NHPs Adverse Reactions to Parmacovigialnce Centre"

Reference Framework			International Frameworks				
Dimension	Attribute	Indicator	Australia	Germany	New Zealand	United Kingdom	United States
5.DataManagement and Assessment of Case Reports	5.1Data Management	5.1.1 Coding of NHPs Adverse Reactions	Yes, MedDRA	Yes, MedDRA	Yes, MedDRA	Yes, MedDRA	Yes, MedDRA
		5.1.2 Existence of Computerized Database	Yes; Australian Adverse Drugs Reactions System (ADRS)	Yes; a database fully compatible with ICH-E2B guidelines	Yes	Yes; called Adverse Drug Reaction On-Line Information (ADROIT) and compatible with ICH-E2B guidelines	Yes; called Adverse Event Reporting System (FAERS) and adheres to ICH-E2B standard guidelines
		5.1.3 Availability of Technology and Standards for Exchange of Information between Stakeholders	No	Yes; Manufacturers are obliged to send reports electronically to the responsible authorities	Yes; a data network is established to share information between authorities and sponsors	Yes; a data network is established through information is shared among stakeholders simultaneously. electronic reporting has become mandatory for companies	Yes; manufacturers are obliged to send reports electronically to FDA for direct database-to-database transmission
		5.1.4 Mechanism to check quality of ADR	Yes; all reports are reviewed within 3 working days of receipt of report	Yes	Yes	Yes	Yes
		5.1.5 A system to conduct Follow-up actions	Yes	Yes	Yes; The reporter are contacted in cases where further clarification or information is required	yes	Yes; by expert committee consist of experts
		5.1.6 Confidentiality and Security	Yes	Yes; The ADR reports are taken strictly in line with the existing confidentiality rules	Yes	Yes; Patients' rights to privacy are guarded by data protection legislation based in European legislation	Yes; the strong protection standards relevance to consumers health information is implemented

Reference Framework			International Frameworks				
Dimension	Attribute	Indicator	Australia	Germany	New Zealand	United Kingdom	United States
	5.2Assessment of Case Reports	5.2.1 Use of causality categories for assessing case reports	Yes: through WHO defined causal categories	Yes: through WHO defined causal categories	Yes: through WHO defined causal categories	Yes: through WHO defined causal categories	Yes: through WHO defined causal categories
		5.2.2 Use of Signal Detection and Data mining Techniques	Yes, Proportional reporting ratio (PRR)	Yes, Proportional reporting ratio (PRR)	Yes, Proportional reporting ratio (PRR)	Yes; PRR and impact analysis	Yes; PRR, Bayesian data mining , case control techniques etc.
		5.2.3 Personalized feedback	Yes; Information on the causality of a reported reaction and management of a suspected ADR via telephone, and, in some cases, further written information about the reported association, can be forwarded to the reporter	NO	Yes; ; Feedback typically consists of the centre's causality assessment, the number of similar reports in New Zealand and/or the WHO, plus any other additional information	No	No
		5.2.4 Provision of Acknowledgement to reporters	yes	Yes; a quick confirmation is send to reporters	yes	Yes; MHRA website automatically generates an acknowledgement letter to all reporters that provides a unique reference number for the case, as well as links to their electronic monthly bulletin, Drug Safety Update	Yes
		5.2.5 Results analyse by multidisciplinary expert groups	Yes; A group of pharmacist, physicians and from other different backgrounds review and assess the submitted ADR reports	yes	Yes; Medicines Adverse Reactions Committee (MARC)	Yes; through a team of physicians, pharmacists, scientists and other expertise members	yes

Table C.5: Comparative analysis for selected countries for "Data Management and Assessment of Case Reports"

Reference Framework			International Frameworks				
Dimension	**Attribute**	**Indicators**	**Australia**	**Germany**	**New Zealand**	**United Kingdom**	**United States**
6. Risk Minimisation and Communication	6.1 Risk Minimization Activities	6.1.1 Periodic education of health professionals	Yes	Yes; through seminars, symposiums and BfArM website	Yes; through workshops, educational seminars and Medsafe website	Yes	Yes
		6.1.2 Tracking urgent/general international safety concerns	Yes	Yes; through EU rapid alert systems	Yes	Yes; through EU rapid alert systems	Yes; FDA participates and monitor safety information through several international alert systems e.g. European, WHO etc.
		6.1.3 Risk management plans (RMPs) from manufacturers	No; there is no requirement for listed and registered NHPs	Yes; for product not falling under the traditional-use registration scheme	No	Yes; for product not falling under the traditional-use registration scheme	No
		6.1.4 Regulatory Authorities requiring Summary reports from NHPs manufactures	Yes; It is important that sponsors continue to prepare annual summary reports in PSUR format but need not to submit until request by the TGA	Yes; in the format of PSURs for product not falling under the traditional-use registration scheme at equal intervals of time	No	Yes; in the format of PSURs for product not falling under the traditional-use registration scheme at equal intervals of time	No
	6.2 Risk communication Tools	6.2.1 A bulletin or newsletter distributed to healthcare Professionals	Yes; six times/year	Yes, four times/year	Yes; three times/ year	Yes; four times/ year	Yes; three times/ year
		6.2.2 Provisions of Website announcements	Yes; regarding product recalls, new and urgent safety information	Yes; regarding market withdraw, changes in product status and safety warnings for public as well as healthcare professionals	Yes	Yes	Yes; Medwatch publish important and timely information on safety issues for consumers and HCP
		6.2.3 Sending Dear	Yes	Yes	Yes	Yes;	Yes

Reference Framework			International Frameworks				
Dimension	**Attribute**	**Indicators**	**Australia**	**Germany**	**New Zealand**	**United Kingdom**	**United States**
		Health Professional Letters					
		6.2.4 Availability of consumer's NHPs information sources	Yes; through TGA website and other NHPs organisations	Yes; through its website	Yes; through Medsafe website, government bodies, consumer health magazines etc.	Yes; through variety of sources	Yes; National Centre for Complementary and Alternative Medicine (NCCAM), FDA etc.

Table C.6: A comparative analysis of selected countries on "Risk Minimisation and Communication"

Appendix D: Best Practices Completely Followed by Canadian Surveillance System

The appendix represents the attributes whose best practices were completely followed by Canadian surveillance system and no gaps were identified in Canadian system.

Dimension	*Attributes*	*Evidence Based Best Practices*
1. NHPs post-market surveillance system structure and stakeholder coordination	1.1 Structure Elements	**Core Best Practices** • The Existence of a regulatory agency or relevant department for NHPs • The Presence of a National Pharmacovigilance Centre including NHPs in their current scope • Existence of a Expert advisory committee on safety of NHPs • Presence of a national research Institute for NHPs
2. Laws and Regulation for NHPs	2.1 Law and Legislation for NHPs	**Core Best Practices** • The existence of a national legislation for regulations of NHPs • The licensing/Registration requirements for both medicinal and non-medicinal claim NHPs • The legal status given to NHPs for sale in the market based upon medicinal/non-medicinal claims
	2.2 Regulations for NHPs manufactures	**Core Best Practices** • The requirement of providing proof of quality and efficacy from manufacturers for medicinal/non-medicinal claim NHPs • The safety evaluations of NHPs prior to marketing for medicinal/ non-medicinal claim NHPs • Obligation on manufacturers to adhere to GMP practices for medicinal/non-medicinal claim NHPs • The Labelling specifications for NHPs manufacturers for medicinal/ non-medicinal claim NHPs • The regulation on control of NHPs advertisements for medicinal/ non-medicinal claim NHPs

Dimension	*Attributes*	*Evidence Based Best Practices*
3. Sources of NHPs Adverse Reaction Information	3.1 Surveillance Approaches	**Core Best Practices** • The Existence of Passive surveillance system for NHPs
4. Reporting of NHPs adverse reactions to Pharmacovigilance Centre	4.1 Reporting Requirements	**Core Best Practices** • Recognising Health Professionals and consumers as volunteer reporters by national reporting scheme • The obligatory reporting requirements for manufacturers to report NHPs adverse reaction to regulatory authorities.
5. Data Management and Assessment of Case Reports	5.1 Data Management	**Core Best Practices** • Use of MedDRA for Coding of NHPs Adverse Reaction • Availability of technology for the electronic Exchange of Information between MAH and regulatory authorities according to ICH standards • A Mechanism in place to check integrity, completeness and duplicates of AR reports • A system to conduct Follow-up actions when the information is incomplete • A national legislation on keeping confidentiality and Security of reporter's identity and information
6. Risk Minimization and Communication	6.2 Risk Communication Tools	**Core Best Practices** • A bulletin or newsletter periodically distributed to healthcare Professionals (5-6 times/year) • Provisions of website announcements to consumers and HCP regarding product withdraw, Recalls, and safety warnings • Sending "Dear Health Professional Letters" in urgent safety issues • Availability of consumer's NHPs information sources

Table D.1: List of best practices completely followed by Canadian surveillance system