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The Impact of the Sentinel Initiative and FAERS Surveillance System on Consumer Safety

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

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Abstract

The U.S. Food and Drug Administration (FDA) uses the FDA Adverse Event Reporting System (FAERS) to monitor adverse events resulting from pharmaceutical drug use. However, this system has limitations such as not allowing real-time data collection. To address these limitations, the FDA launched the Sentinel Initiative in 2008. This comparative case study was conducted to describe perceptions of investigating the efficacy of the Sentinel Initiative compared with the FAERS. The study was based on the theory of preemption as it emphasized the need for efficient means for providing unquestionable proof that consumers suffered adverse drug effects. The sample included interivews of 20 individuals, who worked closely with the FAERS program and were familiar with the Sentinel Initiative. In-depth key-informant interviews had been conducted to determine the perceptions of the participants regarding the challenges and benefits of the Sentinel Initiative compared with FAERS. To analyze data, content analysis was used. The study concluded that the FAERS and Sentinel Initiative provided a systematic database, which included health data, that could be used to improve public health. Due to the FAERS and Sentinel Initiative, adverse effects of drugs will be recognized and the safety of the patients and the public will be prioritized. The findings of this study have potential social impact for positive change at the societal level, organizational level, and individual level in terms of overall safety of the drugs. Sentinel initiative at its present state complements the existing FAERS and leverage its benefits by connecting at a grass roots level patients to an organization level as well as stakeholders to make an impact in providing safer drugs on the market.

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Chapter 1: Introduction

The Institute of Medicine (IOM) identified the mitigation of adverse drug events (ADEs) and medication errors (MEs) as top national priorities. Budnitz, Lovegrove, Shehab, and Richards (2012) found that specific drugs had been reported in 88.3% of emergency hospital admissions of older adults caused by adverse drug events. Identified drugs tied to emergency hospital admissions were hematologic, endocrine, cardiovascular, central nervous system, and anti-infective agents (Budnitz et al., 2012). The findings also revealed that 67% of the hospitalizations were due to unintentional drug overdoses. In particular, warfarin, insulin, oral antiplatelet agents, and oral hypoglycemic agents were found to have accounted for 70% the emergency hospitalizations (Budnitz et al., 2012). According to the Institute for Safe Medication Practices (2014), when it came to children less than 18 years of age, there were 45,610 Adverse Drug Reactions (ADRs) reported for 2012. Of these, 64% reported suffering a serious injury. Reports of children experiencing ADRs also increased over time, from 6,320 in 2008 to 11,401 in 2012, increasing at the same rate as for adult patients (Institute for Safe Medication Practices, 2014).

From 1969 to 2012, the Adverse Events Reporting System (AERS) was the national database used by the Food and Drug Administration (FDA) to support post-marketing drug surveillance (FDA, 2012a). The FDA moved from the legacy AERS to the FDA Adverse Event Reporting System (FAERS) in 2012. As a result, AERS and FAERS were used interchangeably in this study. The referenced sources published before

2012 might refer the surveillance system as AERS while the referenced sources published after 2012 might refer it as FAERS, which was the current FDA reporting system.

The MedWatch report was a reporting system used by patients and health care professionals report problems associated with medicines or medical devices. MedWatch was very important tool for AERS to obtain safety information on medicinal products including medical devices. The same reporting form was used for both patients and health care providers, and the reports could be submitted electronically. The reports obtained from MedWatch could include information for serious adverse events, product problems, and medication errors (Craigle, 2007). In 2011, 874,116 reports were received by the FDA through MedWatch, while only 782,733 out of 874,116 were entered into the AERS. This was a significant increase from 2003 in which only 370,240 reports were received by the FDA through MedWatch (FDA, 2012c).

Background

The public saw the FDA as having a big responsibility in ensuring drug safety (Gavaza et al., 2012). The FDA, however, relies relied on voluntary reporting of adverse events and potential adverse drug reactions because the FDA has had limited resources to support active surveillance (Kip et al., 2013). The AERS served as the main surveillance database used by the FDA used to determine possible safety-related issues of marketed drugs (Wysowski & Swartz, 2005).

Underreporting, differential reporting, and uneven quality were the common limitations of the AERS database; nevertheless, the system-generated reports were often capable of determining serious adverse events to be added to the information on the

product label (Wysowski & Swartz, 2005). Underreporting referred to only a fraction of the total number of reportable events being reported (Zhou et al., 2003). Differential reporting referred to the fact that more serious events were generally reported as well as the events with shorter onset time, such as vaccinations (Zhou et al., 2003). Lastly, uneven quality referred to missing or incomplete data on the adverse reaction or reported event (Wysowski & Swartz, 2005). On rare occasions, additional regulations up to and including market removal had been required by FDA (Wysowski & Swartz, 2005).

Reports submitted to the FDA reporting system often have insufficient detail regarding the consumers who experienced the adverse events or medication errors (Berlin, Glasser, & Ellenberg, 2008; Hochberg, Pearson, O'Hara, & Reisinger, 2009). The AERS was a system that allowed encoding, managing, analyzing, and reviewing adverse event reports from either regulated industry professionals or from the public (Berlin et al., 2008; Hochberg et al., 2009). In response to the limitations of the AERS, the FDA launched the Sentinel Initiative in 2009, which was designed to provide a national electronic-based system to monitor the safety of medical products, including drugs, biologics, and medical devices following the mandate of Congress in the FDA Amendments Act of 2007 (Platt et al., 2012). The Sentinel Initiative includes two components, which were Mini-Sentinel Initiative and the federal partner collaborations (Racoosin, Robb, Sherman, & Woodcock, 2012).

The Mini-Sentinel Initiative, as a part of the pilot phase of the Sentinel Initiative, was an electronic program that involved the participation of many different data partners, wherein each data partner hosted electronic health care information about the medication

people took and their clinical diagnoses. When the FDA had a query for report generation, each data partner would run the exact same query to generate aggregate reports to be sent back to the FDA (Racoosin et al., 2012). To facilitate this process, all data partners had a common data model. The second component of the Sentinel Initiative was federal partner collaboration among the Center for Medicare and Medicaid Services, the Veterans Administration, and the Department of Defense. These federal partners administered or ran a population specific health care system (Racoosin et al., 2012). Given the limitations of AERS, including the application of the Sentinel program, the FDA moved from the legacy AERS to the FDA Adverse Event Reporting System (FAERS) in 2012. FAERS contained data encoded into the system since 2004. The data were presented at the individual report level with potential duplicates due to factors such as follow-up reports on a case.

There was a need to assess the benefits and challenges of surveillance methodology associated with the FDA's Sentinel Initiative compared to FAERS. The aim was to conduct a comparative case study of the current FAERS surveillance system and the FDA's Sentinel Initiative to determine the impacts and benefits of the Sentinel Initiative in terms of consumer safety. A summary of the attributes of the FAERS and the Sentinel Initiative is presented in Table 1.

Table 1

FAERS and Sentinel Descriptions

	FAERS	**Sentinel**
Function/Purpose	To report the adverse effects of drugs and to provide a database for these reported cases of adverse drug reactions	To develop and implement a proactive system that would complement existing systems that the agency had in place to track reports of adverse events linked to the use of its regulated products
Size/Capacity	Depend on information reported by consumers, Health Care Professionals etc.	Utilized existent large number of databases containing safety information
Activities	Report generation regarding errors in medication. Information storage on adverse events Support for FDA's post-marketing safety surveillance program for drug and therapeutic biologic products	Query diverse automated health care data holders to evaluate possible medical product safety issues quickly and securely
Limitations	There was no certainty that the reported event was actually due to the product (FDA did not require a causal relationship between a product and event). The quality of reporting was dependent on the quality of the reports. Reports did not always contain enough detail to properly evaluate an event. FDA did not receive reports for every adverse events	There were some data that might be missing in the database to facilitate activities other than analysis of errors in medication (e.g., filing of claims).

Problem Statement

The current FDA consumer safety surveillance system used FAERS for the reporting of adverse events involving pharmaceutical drugs (FDA, 2012a; Powers & Cook, 2012;). The FAERS used a database that was designed to assist the FDA and its partners to monitor postmarketing safety of approved drugs and other biologic products (Powers & Cook, 2012). The FAERS had limitations including not allowing real time data collection (FDA, 2012a). In response to these limitations, the FDA launched the Sentinel Initiative in 2008. However, there is a dearth of literature regarding the impact of Sentinel Initiative compared to the FAERS. There is a need to assess the benefits and challenges associated with the FDA's Sentinel Initiative compared to the current FAERS surveillance methodology.

This comparative case study was conducted to assess the impact of two systems: the Sentinel Initiative and FAERS. According to the FDA (2012a), the FAERS had two functions: (a) a system for reporting the adverse effects of drugs, and (b) a database for these reported cases of ADRs (FDA, 2012a). As for the Sentinel Initiative, the function was to build and implement a national electronic system for monitoring the safety of FDA-approved drugs and other medical products (FDA, 2012d).

The FAERS and the Sentinel program were both ADR reporting systems. The Sentinel system was developed and implemented as an aid to the existing FAERS. The FAERS did not make use of data at the point of care, which referred to the precise time or location that a drug was used or consumed by the market members (Gottlieb, 2005). According to the FDA (2012b), "The Sentinel System enables FDA to actively query

diverse automated healthcare data holders—like electronic health record systems, administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely" (para. 2).

Purpose of the Study

The purpose of the comparative case study of the FAERS surveillance system and the FDA's Sentinel Initiative was to determine the benefits and consequences of the Sentinel Initiative in terms of drug consumer safety. This qualitative study focused on the perceptions of individuals who had worked closely with FAERS program and were aware of the Sentinel Initiative. Key informants were interviewed who worked with FAERS andwere familiar with the Sentinel Initiative to understand their perceptions of the differences between these two programs.

Currently, the reporting system utilized by the FAERS is voluntary and quarterly (Powers & Cook, 2012). Instead of depending on point of care data collection, Sentinel Initiative could access multiple existing data systems such as electronic health record systems and medical claims databases (Platt et al., 2009). No quantification of data was carried out to compare information on the two programs. Instead, the perceptions of key informants were used to describe any differences between the two programs.

Research Questions

In conducting a comparative case study on the perceptions of the two systems that the FDA used to detect ADRs, these following research questions were used:

Research Question 1: What are the prospective benefits of the FDA's Sentinel Initiative as compared with the FAERS surveillance methodology?

Research Question 2: What are the challenges and negative impacts of the FDA's Sentinel Initiative as compared with the FAERS surveillance methodology?

Research Question 3: What are the lessons learned that can enhance the scope of the Sentinel Initiative?

Theoretical Framework

The theory of preemption was used to frame the study. The theory of preemption assumes the importance of using information to make sound judgments regarding issues or activities of national importance, such as prescription drug-related regulations or required uniform federal regulation, which cannot be provided by states (Deftos, 2008; Glantz & Annas, 2008). The theory of preemption is used to analyze data from ADRs and cases to address the damages experienced by affected consumers (Valoir & Ghosh, 2011).

The theory of preemption might shield drug manufacturers from certain liabilities when consumers experience adverse effects from their products (Curtin & Relkin, 2007). Court rulings and federal decisions had shown support for the protection of drug manufacturers who faced allegations of adverse drug effects from their consumers (Curtin & Relkin, 2007). Preemption prevented state courts from assessing the safety and efficacy of a drug when it came to a personal injury products liability lawsuit, thereby giving drug manufacturers the ability to avoid litigation even if the patient who suffered from ADR had already filed a complaint against the company to the FDA (Shniderman, n.d.).

The theory of preemption was important in framing the study as it emphasized the need for efficient means for providing unquestionable proof that consumers suffered adverse drug effects. Because this studyfocused on the comparison between two surveillance and reporting systems with the goal of improving drug safety, the theory of preemption was the most appropriate theoretical framework for the study. Under the theory, the FDA required current, accurate, and actionable information to ensure consumer safety, especially in detecting uncommon cases of product exposures (Platt et al., 2009).

Nature of the Study

This comparative case study design waswas qualitative in nature. Qualitative methodology was appropriate for this study because qualitative studies are used to explore a phenomenon within its natural environment (Yin, 2011). Moreover, a comparative case study design was appropriate because the aim was to explore the differences and similarities between two cases, (a) use of FAERS and (b) use of Sentinel Initiative, based on the perspectives of participants (Yin, 2011). In-depth key-informant interviews had been conducted to determine the perceptions of the participants regarding the challenges and benefits of the Sentinel Initiative compared with FAERS. The data analysis technique used was content analysis. Krippendorff (2004) stated that content analysis involved the development of thematic categories and themes from qualitative data. Open coding was used to analyze the data to extract the key themes related to the research questions.

Key informants included drug company safety professionals who had self-reported knowledge or expertise in assessing consumer impact. The participants were selected from various departments within pharmaceutical companies located in the United States. The participants were subject matter experts in the field of pharmacovigilance. Sampling involved participants at different levels from different therapeutic departments such as pain and inflammation, cardiovascular, and psychiatric and mental health.

Definitions

Adverse drug reaction (ADR): "Any response to a drug, which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy" (van Grootheest & Richesson, 2012, p. 368).

Pharmacovigilance: "The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems" (World Health Organization [WHO], 2014, para. 1).

FDA Adverse Event Reporting System (FAERS): An information database system which was acted as the post-market monitoring system for the FDA. FAERS used historical data or information to supervise new adverse events and medication errors from drug and therapeutic biologic products (FAERS, 2012a).

FDA Sentinel Initiative: A national electronic system that allowed the FDA to comprehend and ensure the safety of specific medical products (FDA, 2012b).

Assumptions

There were several assumptions in the study. The first was that the participants would answer each question in the interview as truthfully and accurately as possible. This was a necessary assumption because this could not be controlled fully; however, before the interview started, the participants were reminded of this. The second assumption was that the two programs were comparable, especially because they dealt with the same issues, specifically adverse event reporting. The third assumption was that the both programs had benefits and challenges to determine room for improvement as part of the implications of the study findings.

Scope and Delimitations

The perceptions of the participants were gathered regarding the challenges and benefits of the Sentinel Initiative compared with the FAERS. Interviews were conducted with participants who met the inclusion criteria: (a) safety professionals from drug companies and (b) had self-reported knowledge or expertise in assessing consumer impact.

Limitations

There were many limitations in this study such as sample size, researcher bias, and data collection bias. Each limitation had an impact on this study and every effort was made to control the effects of the limitations. One limitation was researcher bias. I have extensive knowledge of Adverse Drug Reactions (ADRs) and pharmacovigilance systems. To mitigate this bias, data collected was examined during participant interviews as is and conducted member checks to ensure that the interpretations made were

consistent with the actual interpretations intended by the participants. This limitation might have had an effect on the interview questions used for data collection. Recognizing this, the questions were written without bias to allow the participants to use their experiences and knowledge to answer the questions.

Another limitation was the possibility of not obtaining enough participants. Key informants included drug company safety professionals who had self-reported knowledge or expertise in assessing consumer impact. Another factor that might have resulted in inadequate results was poorly developed interview questions. The interview guide must be developed properly to be open ended yet specific enough to avoid confusion. To avoid this pitfall, proper considerations were given in developing the interview guide. Another limitation was sample size selection. The study was limited to sample 20 participants with the consideration of data saturation. The required sample size for qualitative studies was based on the point of data saturation (Mason, 2010).

Social Significance

This study definitely may have potential to increase awareness of advantages and disadvantages of the FAERS and the Sentinel Initiative programs. It was expected that the data would provide information regarding the effectiveness of the FAERS and the Sentinel Initiative. This study may increase public knowledge of the reporting systems used by the FDA to control ADRs. The lessons learned from this study may be used to support the FDA's efforts to improve reporting systems' effectiveness to detect ADRs. This current study may also add to the research base regarding pharmacovigilance systems. Moreover, with the findings of the study, the benefits and challenges of the

FAERS and the Sentinel systems may serve as basis for further improvements to the programs. As a result, health and quality of life may be improved because the challenges of the programs on ADR generation may be identified for ease of addressing them. It could support the FDA's efforts to improve reporting systems effectiveness to detect ADRs.

Summary

The occurrence of ADRs in the United States had increased in the past decade (Yadav, 2009). ADRs were costly and could have a negative impact on public health programs that detect ADRs (Yadav, 2009). Furthermore, ADRs were among the leading causes of death in many countries, including the United States. According to Keating and Millman (2014), from 2004 to 2012 men and women reported 60,000 deaths. Despite the similarities in their numbers, death was the number one ADR among men, while it was the ninth among women. Pharmacovigilance systems were used to detect and prevent ADRs. The purpose of this qualitative comparative case study was to compare two ADR reporting systems to determine whether one was more effective than the other. This investigation might lead to a better understanding of the effectiveness of the ADR reporting systems and assist the FDA with improving ADR surveillance and reporting. The next chapter presents a detailed review of related literature.

Chapter 2: Literature Review

The purpose of this comparative case study of the US Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) surveillance system and the FDA's Sentinel Initiative was to determine the benefits and consequences of the Sentinel Initiative in terms of drug consumer's safety. Instead of depending on point-of-care data collection like the FAERS surveillance system, the Sentinel Initiative accessed multiple existing data systems, such as electronic health record systems and medical claims databases (Platt et al., 2012). Perceptions of the perceived challenges and benefits of FAERS and Sentinel Initiative were gathered through key informant interviews with individuals who worked with FAERS and were familiar with the Sentinel Initiative. Robb et al. (2012) described the mission of the FDA as providing health protection to the public. To do this, the regulatory body ensured the safety, efficacy, and quality of the human drugs. Aside from human drugs, the FDA also regulated the quality and safety of biologic products, medical devices, and more (Robb et al., 2012).

For years, the regulating body was dependent mostly on spontaneous reporting systems to complete its task of monitoring post-market safety. The FDA relied heavily on the public, practitioners, and consumers to voluntarily report adverse drug effects, errors, and other quality problems either to the FDA or directly to the drug companies. Although manufacturers were mandated by law to report to the FDA when adverse events were reported to them, the FDA still required active public participation in reporting such occurrences. Naturally, these spontaneous reporting approaches for ADRs had their limitations (Robb et al., 2012).

One of the weaknesses of such an approach was the underreporting of adverse events and incomplete information on the reports submitted to the FDA. Moreover, even though these systems were strong for developing hypotheses regarding possible product-associated adverse events, the number of events being reported did not accurately represent the actual number of cases of ADRs (Alvarez-Requejo et al., 1998). Aggravating this was the lack of exposure data, which served as a barrier for accurately calculating adverse event rates. The FDA was aware of these limitations and continued to strive for stronger post-market safety monitoring. The literature review begins with the history of the FDA and its role in ensuring drug safety, followed by studies covering ADR surveillance using FAERS and the Sentinel Initiative.

Literature Search

To conduct the literature review, relevant studies were searched that contributed to the development of the research topic for this study. The databases used for this study were EBSCOHost, PsychArticles, ProQuest, and ScienceDirect. The key words used included *adverse events reporting system*, *surveillance system*, *FAERS*, *FDA Sentinel Initiative*, *pharmacovigilance*, and *ADR*. The search for articles was focused on works published from 2009 to 2014, with exceptions for seminal works that were essential to the development of the study. The key words were used in the database search as individual and combined terms to identify appropriate articles for this literature review.

Theoretical Framework

The theory used to frame this study was the theory of preemption, which is based on the supremacy clause of the U.S. Constitution and can be applied to state statutes,

regulations, or common-law damage actions. When it comes to preempting common-law damage actions, the plaintiffs cannot sue for damages regarding injuries caused by a product. Preemption is considered an affirmative action, which means the burden of proof lies with the defendant to adhere to the preemptive effect of the federal law (Shniderman, n.d).

Because the theory of preemption involves the use of data to make market-based decisions regarding drug safety (Gostin, 2011), the theory of preemption was the most appropriate theoretical framework for the study, which focused on the comparison between two surveillance and reporting systems with the goal of improving drug safety. The theory of preemption is used with quantitative data from adverse drug effect reports and cases to address the damages experienced by affected consumers (Gostin, 2011). According to Gostin (2011), the two cornerstones of the preemption theory are Congress's intent to be the ultimate touchstone and the "strong presumption against preemption when the state exercises its historic police powers" (p. 11). Because of this doctrine, even though the FDA was viewed as ineffective and even if ineffective drugs and devices were being marketed, consumers had limited recourse to be fairly compensated for their injuries (Gostin, 2011).

The theory of preemption shields drug manufacturers from certain liabilities when consumers experience adverse effects from their products (Shniderman, n.d.). Preemption is often the position taken when an injury to a patient or plaintiff is reportedly caused by prescription drugs (Shniderman, n.d.). Under this theory, the approval process is the focus and not the post-approval sales. For the FDA, product liability lawsuits can threaten

the agency's capabilities in regulating risk information for prescription drugs. Under preemption, the FDA is considered to have the requisite expertise to deal with issues of safety and efficacy of prescription drugs. The FDA argued that approval of drugs' label demonstrated the agency's definitive judgment of certain risks and this judgment should be protected from second-guessing (Kessler & Vladeck, 2008). Recent court rulings and federal decisions had shown much support for the protection of drug manufacturing companies who faced allegations of adverse drug effects from their consumers (Curtin & Relkin, 2007). This theory was important in framing and shaping the significance of this study as it emphasized the need for efficient means of providing unquestionable proof that consumers suffer adverse drug effects.

Evolution of FDA and Drug Safety

History of Drug Safety

Ensuring the safety of the food supply and safeguarding the public from the practice and effects of adulteration and misleading marketing was probably the earliest regulatory task undertaken by ancient governments, and when the Roman civil law was established, there were already complex rules addressing these issues (Borchers, Hagie, Keen, & Gershwin, 2007). In the United States, such regulatory activities were originally under the auspices of the state. No federal food laws were designed until the 1880s, when Congress started to enact statutes regulating individual food items, such as the laws banning the importation of adulterated tea, limiting the manufacture of oleomargarine, and inspecting meat produced for exportation (Borchers et al., 2007).

The history of federal drug laws could be observed to go back further. In 1813, Congress put into place the Vaccine Act, which was the first statute facilitating the regulation of adulterated drugs. Afterward, a more general federal law on drug adulteration was called for. The U.S. -Mexican war had just ended, and members of Congress were convinced that adulterated and decayed foods and drugs explained why there was a high mortality of soldiers in this war (Borchers et al., 2007). Although many soldiers of the U.S.- -Mexican war died because of the infectious diseases and general inadequacy of medical treatment, Congress was convinced that adulterated and inferior drugs played a large role in the high mortality rate of the soldiers, and this conviction led to the passage of the Drug Importation Act of 1848. The Treasury Department acquired the responsibility of enforcement but found it difficult over time. In addition, one weakness of the law was that it only addressed the importation of adulterated drugs and not their manufacture and sale within the United States (Borchers et al., 2007).

The Division of Chemistry investigations began in the mid18th century, and Wiley, who became chief chemist in 1883, greatly influenced the U.S. government to take on the adulteration and misbranding of foods and drugs. Wiley published a 10-part study in 1887 called “Foods and Food Adulterants,” and in 1902 conducted famous poison squad experiments in which volunteers would take food additives to see their reaction (Borchers et al., 2007). Wiley then convinced the General Federation of Women’s Clubs, consumer groups, trade associations, professional groups, and state food and drug officials to stand behind a federal law prohibiting adulteration and misbranding of foods and drugs (Borchers et al., 2007).

Role of FDA in Drug Safety

When the 19th Century ended, many infectious diseases were discovered. Antitoxins and vaccines could treat and prevent the diseases. However, in October and November 1901, 13 children died because of inoculation with a diphtheria antitoxin contaminated with tetanus bacillus (Borchers et al., 2007). As an immediate response, Congress and President Theodore Roosevelt passed the Biologics Control Act of 1902 mandating that establishments wanting to produce and sell market vaccines and antitoxins should have the required licenses. This was facilitated by the Public Health and Marine Hospital Service, now known as the U.S. Public Health Service (Borchers et al., 2007).

The Wiley Act, or the Pure Food and Drugs Act of 1906, banned interstate commerce in adulterated foods, drinks, and drugs. The Act mandated that producers should put labels on their products that indicated whether the medication consisted of "alcohol, opium, cocaine, morphine, chloroform, marijuana, acetanilide, chloral hydrate, and in what amount" (Borchers et al., 2007, p. 6). However, while the Wiley Act prohibited false and misleading statements on the product or its ingredients, the Act did not consider advertising material as part of the label. This created vagueness of the Act. Nevertheless, the Act was commended for establishing the role of the federal government as the protector of consumers. Moreover, the Wiley Act created the first federal regulatory agency that would later become the FDA. Wiley, who was the head of the Bureau of Chemistry, took on the role of the first chief administrator of this new agency (Borchers et al., 2007). The Wiley Act, however, was complex to enforce partly because

there was insufficient budget and partly because the Bureau of Chemistry had to bring each company to court to prove adulteration, mislabeling, or other violations. While the Act put forward what was fraudulent (misleading the consumer), it was not easy to prove fraudulence took place (Borchers et al., 2007).

The FDA petitioned for changes in laws, which "legally mandated quality and identity standards for foods, the prohibition of false therapeutic claims for drugs, coverage of cosmetics and medical devices, clarification of the FDA's right to conduct factory inspections and control of product advertising, among other items" (Hickmann, 2003, p. 11). Together, the FDA and a new generation of journalists and consumer organizations banded together in attempts to influence the passing of this new legislation through a reluctant Congress (Hickmann, 2003, p. 11). Unfortunately, it was another therapeutic disaster that propelled the legislation through Congress, for in 1937, a Tennessee drug company marketed elixir sulfanilamide, which was popular in the pediatric population. This sulfa drug contained a chemical found in antifreeze; as a result of the substance, more than 100 people died, most of them were children (Hickmann, 2003, p. 183).

Because of the Tennessee drug company tragedy, Congress enacted the Food, Drug, and Cosmetic Act on June 25, 1938. This Act regulated cosmetic and medical device and requirement of label medication with usage instructions. In addition, pre-market approval from the FDA was another big initiative that enhanced safety and efficacy of drugs. Another positive change resulted in the area of food packages, food quality, and its standards. This law authorized the FDA to inspect factory facilities and

enforce other safety requirements per the agency's guidelines (FDA, 2012d). In addition, in 1938, another therapeutic disaster spawned the creation of the Kefauver-Harris Amendments. Thalidomide, a sedative that was used outside of the United States, had caused thousands of deformed newborns. The Kefauver-Harris Amendments also provided for drug efficacy and safety evaluation by the FDA before marketing, stricter regulation of drug trials, improved drug manufacturing practices, and the empowerment of the FDA to assess drug company production and control records (FDA, 2009).

In 1960, more than $1 billion dollars of medical devices were shipped by more than 1,000 manufacturers. In the early 1970s, approximately 10,000 injuries were documented by government because of usage of these medical devices. However, after causing more than 200-second trimester septic abortions and 11 maternal deaths, the Dalkon Shield intrauterine device was withdrawn from the market. In response to this and other events, Congress enacted the Medical Amendments of 1976 to ensure the FDA's ability to maintain safety and effectiveness of medical devices entering the market (Maisel, 2004). The legislation was founded on the idea that the degree of device regulation should correspond to the degree of risk one could be exposed to by using the device. As a result, the FDA pre-market evaluation and approval, carried out by the Center for Devices and Radiologic Health, was largely determined by what the device was and the level of risk perceived to the patient's health (Maisel, 2004).

The legislation included three regulatory classes. This new legislation divided medical devices into three tiers based on the risk posed by the device. Class 1 (low risk devices) medical devices operated under FDA general controls and included products

such as stethoscopes and tongue blades. Because they posed minimal risk, their safety and effectiveness were maintained through general controls only (Maisel, 2004). Class 2 (moderate risk devices) medical devices functioned under FDA performance standards and consisted of such products as computed tomography scanners and gastroenterology endoscopes. Class 2 devices were regulated by making sure they met or even exceeded specific predefined product performance standards (Maisel, 2004). Class 3 devices (higher risk devices) such as pacemakers and silicone breast implants were the most heavily regulated and require the FDA's premarket approval (Maisel, 2004). The safety and effectiveness of Class 3 devices were maintained by carrying out a comprehensive and thorough pre-market evaluation and approval process (Maisel, 2004).

According to Maisel (2004), for devices to be stamped with FDA approval and enter the United States market, manufacturers should first show that the device was safe by proving the possible risks were minimal or the benefits would outweigh the risks. Manufacturers should also show that the device was effective by proving that it could do what it committed to do for users. Manufacturers must show data that supports their safety and effectiveness claims, which might include verification and validation studies, observational studies, randomized clinical trials, manufacturing tests, and statistical risk analyses (Maisel, 2004). The manufacturer would choose evidence based on what was required by the FDA to determine safety and effectiveness, which was largely dependent on the type of device and what it had promised to users. The perceived risk of the user's well-being was also a factor determining what evidence the FDA would ask for. For example, if a device was manufactured with the intention of treating a life-threatening

condition for which no alternative existed, the FDA might consider the device as having a higher acceptable risk compared to devices that were manufactured with the intention of treating a benign condition (Maisel, 2004). Congress called for the FDA to use the "least burdensome approach," which meant the FDA should only require manufacturers to provide the necessary data for them to prove the safety and effectiveness of their devices (Maisel, 2004).

Under this new regulation, devices were approved by the FDA and entered the market in either of the two ways: first, by showing substantial equivalence to an already approved and legally marketed device and second, by providing data as evidence of safety and effectiveness through the Pre-market Approval Application (Maisel, 2004). Devices that posed only minimal risk were exempted from intense scrutiny and might only need to be subjected to registration and listing with the FDA. Others might only require evidence that they had passed compliance with manufacturing guidelines. The FDA put forward Guidance documents, which summarized what manufacturers need to provide and show before their devices were approved (Maisel, 2004). According to Borchers et al. (2007), the evolution of FDA could be characterized as a series of "crisis-legislation-adaptation cycles." It was always a crisis that triggered a legislation to be made and followed by the implementation or adoption of the FDA legislation.

Pharmacovigilance

Pharmacovigilance referred to science and activities linked to detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO, n.d.). Pharmacovigilance activities encompassed the collecting,

exchanging, accumulating, analyzing, interpretation and sharing of data regarding the experiences of patients who had used a specific drug or certain therapeutic agent. Pharmacovigilance played an important role in ensuring drug safety and the activities associated with it had become increasingly scrutinized by the drug industry (van Grootheest & Richesson, 2012, p. 368). According to van Grootheest and Richesson (2012), pharmacovigilance and drug safety monitoring activities could shape clinical research practices significantly. Most pharmacovigilance and population monitoring activities were also clinical research studies themselves, so that they could also affect research and development activities. The findings of pharmacovigilance and drug safety monitoring activities could led to improved decisions by treatment agent manufacturers as well as improved future trials (van Grootheest & Richesson, 2012).

If there were no systematic detection and assessment practices in place that could deal with adverse drug effects, thousands of individuals might suffer from side effects of the drugs they used before a clinician could be subjected to public investigation and action (van Grootheest & Richesson, 2012). An adverse event was a clinical event, sign or symptom that deviated from the wanted results. No concept of causality had been asserted with adverse events. On the other hand, an ADR implied causality or a causal relationship between the drug and the event. One was the probable cause and one was the effect. If an ADR were suspected, then trials and tests would have to be carried out in order to confirm or refute the suspicion. Before tests were carried out, careful and systematic collection of data was necessary (van Grootheest & Richesson, 2012).

The decision to ban thalidomide from the market was the result of actively collecting data and cases of adverse reactions to the drug. This case also propelled the FDA to start a systematic collection of ADR reports, mainly through the Hospital Reporting Program. The case also led to different countries establishing policies that would regulate new drugs, which composed of new rules and regulations that new drugs have to meet before receiving marketing authorization. Moreover, marketing authorization holders were commissioned to form a system focused on post-marketing surveillance so that ADRs could be detected as early as possible and prevented a similar case as the thalidomide from taking place (van Grootheest & Richesson, 2012). In 1968, 10 countries that supported the spontaneous reporting system of ADRs collaborated to establish International Drug Monitoring (Lindquist, 2003). In 1971, the 20th World Health Assembly proposed the foundations for the WHO International Drug Monitoring programme (van Grootheest & Richesson, 2012). In 1972, a report was written to serve as the foundation for the international system of national centers working together under the WHO programme (van Grootheest & Richesson, 2012).

Even though these sophisticated programs and models had changed through time, the motivation and main strategies behind pharmacovigilance had not changed. The main motivation to carry out pharmacovigilance was still to ensure public safety and the main strategy was still population monitoring (van Grootheest & Richesson, 2012). In addition, the overall goal of pharmacovigilance was to balance the risks associated with a drug to the benefits that could be gained from it. Pharmacovigilance sought to balance the risk-benefit ratio of drugs for the public. It perceived that all therapeutic agents had a specific

level of risks and these risks were not equally distributed across the population. Some groups were more likely to suffer from ADRs compared to others (van Grootheest & Richesson, 2012). Pharmacovigilance did not deny the possibility of risks associated with certain drugs and more importantly; it was cognizant that individual variations that could affect the course of a disease should be taken into consideration. Individual variations also dictated the preferences of treatment options and an individual's tolerance of side effects (van Grootheest & Richesson, 2012).

According to Raine (2012), harmful effects from drugs should be monitored, as they could be deadly and costly to the healthcare sector. The costs were high in developed countries, but could be even greater in developing countries (Raine, 2012). For these countries, even if only a few patients suffer real harm from ADR, these incidents might cause significantly negative consequences on the credibility and success of important public health programs (Raine, 2012).

Such situations highlighted the need for pharmacovigilance, which was the science and method of detection, assessment, and comprehension of adverse drug related problems. To enhance pharmacovigilance strategies, the WHO claimed that more emphasis must be given to the planning and implementing of ADR surveillance systems (Raine, 2012).

Methods in Pharmacovigilance

There were various methods used in detecting new ADR, categorized into pre-marketing and post-marketing studies. The primary method of gathering information regarding a drug before it was marketed was the carrying out of a clinical trial (van

Grootheest & Richesson, 2012). Double-blind randomized controlled trials comprised the most comprehensive method of determining the possible cause-effect relationship between a treatment agent and a specific outcome. This study was not completely effective in determining the safety of a drug, especially because only limited number of patients participates. This made it impossible to determine rare ADRs as a result. Moreover, the short period on which clinical trials were carried out made it challenging to identify ADRs with a long latency (van Grootheest & Richesson, 2012). The effectiveness of clinical trials was also questionable when the population in which a drug was tested was taken into account (van Grootheest & Richesson, 2012).

Specifically, the problem lied with the fact that characteristics of the persons to which this drug was tested would not always correspond to the characteristics of the people who would actually use the drug. This made it harder to generalize findings gathered from clinical trials to the population at large. This could be especially observed among the elderly, women and with disabilities (van Grootheest & Richesson, 2012). Rare ADRs therefore could be detected more with post-marketing studies rather that tests carried out before the drugs were carried out. Careful monitoring of the drug and its effects after they had been released to the market was necessary (van Grootheest & Richesson, 2012).

Post-marketing studies could be either descriptive or analytical (van Grootheest & Richesson, 2012). The former type of post-marketing studies could lead to hypotheses that would describe how events occurred in relation to the toxicity of the drug as well as its effectiveness. Causal relations therefore could be depicted through this. Under post-

marketing surveillance, the hypotheses generated from the descriptive studies served as the starting points of analytical studies (van Grootheest & Richesson, 2012). Spontaneous reporting as well as intensive monitoring were the two dominant types of descriptive studies. On the other hand, there were different methods to carry out analytical studies such as case-control studies, cohort studies, clinical trials and more others. Most of these studies could only be carried out if there were already reliable data available (van Grootheest & Richesson, 2012).

A spontaneous reporting system (SRS) such as FAERS was considered the main method of gathering post-marketing information regarding the safety of drugs. SRS were designed to detect signals of new, rare, as well as significant ADRs as early as possible. By having an organized spontaneous reporting system, parents, physicians, and the patients would all have the opportunity to reported ADRs as early as the day they had suspicions to a pharmacovigilance center (van Grootheest & Richesson, 2012).

The pharmaceutical companies also made use of SRS to research their own drugs. The SRS enabled them to monitor their drugs at their whole life cycles for minimal costs (van Grootheest & Richesson, 2012). However, SRS were critiqued for their selective and underreporting. According to a study, where the researchers evaluated the magnitude of underreporting, more than 94% of ADRs were not being reported. Because of this underreporting, FDA, the pharmaceutical companies, and the public had a misconception that the specific drug was safe. On the other hand, selected reporting of risks could lead to the misconception that a specific risk existed when there was none (van Grootheest & Richesson, 2012).

Still, even though criticisms abound, it had proven its value throughout the years. From 1999 to 2011, 11 drugs were withdrawn from the American and British markets, which were two of the globally prominent markets. This showed how valuable SRS was. Among the 11 drugs, eight were removed because of the findings shaped by and because of spontaneous reporting (van Grootheest & Richesson, 2012). The WHO gave importance to spontaneous reporting systems as an important part of pharmacovigilance, given their capacity to reduce the risk of drug-related problems (Raine, 2007). According to Herdeiro et al. (2012), spontaneous report methods were the most dominant form of reporting ADRs. However, this method was prone to physicians' underreporting (Herdeiro et al., 2012).

To address this concern, Herdeiro et al. (2012) conducted an experiment to see if particular interventions could help increase instances of physicians reporting ADRs. Herdeiro et al. (2012) compared the results of workshops and over-the-phone interview interventions designed to enhance the quantity and relevance of ADR reporting by physicians. Herdeiro et al. (2012) performed a cluster-randomized controlled trial, wherein 6,579 physicians from northern Portugal were gathered to participate in 2008. After conducting randomization, Herdeiro et al. (2012) put 1,034 physicians in a group conducting telephone-interview interventions, and 438 in a group under the category of workshop intervention. The remaining physicians were categorized as the control group (Herdeiro et al., 2012).

At the workshop, a real clinical case was demonstrated and the physicians were asked to report on it by completing the necessary forms (Herdeiro et al., 2012). In the

over-the-phone intervention, the physicians answered questions pertaining to whether they had ever suspected ADRs and whether they suffered any challenges when it came to reporting these (Herdeiro et al., 2012). They were also asked whether they could recall the methods for reporting ADRs and whether they found it important that they, as physicians, had a hand in the reporting process, faced difficulties in reporting, propose different method of reporting, or value reporting adverse events (Herdeiro et al., 2012).

Statistical analyses of data from all groups revealed that the workshop intervention had the ability to increase spontaneous ADR reporting rates by an average of 400% up to 20 months after intervention (Herdeiro et al., 2012). On the other hand, telephone interventions were not found as efficient or effective. They led to no significant increase in spontaneous ADR reporting in comparison to the control group (Herdeiro et al., 2012). Still, for the first four months, telephone interventions did increase spontaneous reporting (Herdeiro et al., 2012). Based on the study of Herdeiro et al. (2012), it could be concluded that interventions in general could improve spontaneous ADR reporting. However, workshops were better at increasing both the quantity and relevance of spontaneous ADR reporting for a longer time.

Lorimer, Cox, and Langford (2012) analyzed the influence of ADRs on patients and their views on reporting. The researchers interviewed the patients who experienced an ADR and were admitted in an inner city hospital. The researchers found that most of the patients were afraid of being admitted to the hospital. More than anyone, they expected the healthcare professional to prescribe the medication that would not cause harm and to be the expert medication treatment (Lorimer et al., 2012). The patients rarely

read the patient information leaflet. As such, when an adverse reaction occurred after taking a medication, few of them associated the adverse effects with the medication. Some of them, however, received false reassurance that the drugs were not behind the adverse event or the illness. These factors led to additional barriers to accurate reporting of adverse reactions. A majority of the patients believed that adverse drug reporting should not be their responsibility (Lorimer et al., 2012).

From the 1970's to the 1980's, intensive monitoring had emerged as another descriptive method of identifying ADRs in New Zealand and the UK, which was called Prescription Event Monitoring. Under this method, prescription data was utilized to determine who the users of a specific drug were. The prescriber was questioned on any incidences of adverse event that took place when the drug had been in use. The data gathered from the prescriber were considered as new signals (van Grootheest & Richesson, 2012). The benefits of intensive monitoring were many. First, the findings of this method were not affected by the kind of selection and exclusion criteria the same very clinical trials were. Moreover, because identification of ADRs was done through monitoring, this could result into the identification of signals for events that were not initially perceived as ADRs of the drug being monitored. In addition, this method could lead to the estimation of how frequent the ADRs of a certain drug took place, thereby made it possible to quantify the risks of ADRs (van Grootheest & Richesson, 2012).

When a new drug was approved, its safety could only be ascertained through the responses of the several thousand people who took it during clinical trials. However, once it entered the market, the real safety testing got under way. Within a year or two of

introduction, the number of people who were exposed to the medication and its effects might rise significantly into millions, especially if the drug manufacturer practices rigorous and aggressive marketing and advertising through television, print and more others (Okie, 2005). If the drug had dangerous and yet unusual side effect, for instance, liver failure that was only suffered by one in 1000 patients, that effect would normally be acknowledged and determined only after the medication had already been taken by millions of users. In addition, if the drug increases the occurrence of a common condition, for instance, myocardial infarction, this risk could only be recognized after a million of people had used the drug as well (Okie, 2005). Almost 50% of the drugs that were introduced to the market had serious adverse effects that were only recognized once they were already approved (Okie, 2005). What was worse that most Americans were usually the test population. Because of the quicker review of product applications conducted by the FDA, at least 60% of new drugs were always approved first in the United States, unlike decades ago, when drugs were often approved in other countries (Okie, 2005).

This shift led to a parallel increase in the attention given by experts, lawmakers, consumer advocates and federal officials to drug safety. They call for better ways of monitoring the effects and safety of already approved drugs (Okie, 2005). The fact that more Americans were taking prescription drugs served to make the calls more urgent. In 2004, pharmacists had filled 3.1 billion prescriptions, around 60% of which were more than 10 years earlier. Reports to the FDA of drug-related adverse reactions had also heightened correspondingly and now total of 375,000 annually, more than double the

number a decade ago (Okie, 2005). These figures were alarming considering the agency's current surveillance system was passive, depending on the diligence of drug companies only, as well as the reports of healthcare providers and consumers (Okie, 2005).

According to policy experts, a new system should be in place to obtain observational data on significant numbers of people who were vulnerable to medications being introduced to the market (Okie, 2005). The information might be collected from databases as they were increasingly accessible through many managed-care networks and other providers shifted to the use of electronic medical records (Okie, 2005). According to Kuehn (2012), IOM called for the FDA to be more aggressive and proactive in responding to the safety concerns that emerged after a drug had been introduced to the market.

Based on the study of Dart (2009), the main purpose of post-marketing surveillance was for the FDA to provide accurate information on the risks associated with a drug. Drugs that affect the central nervous system comprised a group of products that should be surveyed because they were usually used inappropriately either by misusing them, abusing them or diverting them (Dart, 2009). Examples of these medications were opioid analgesics, stimulants, sedative-hypnotics, muscle relaxants, anticonvulsants and more other drugs (Dart, 2009). The adverse events associated with these drugs were complex to monitor because the perpetrator was usually determined to hide the misuse, abuse and diversion of the drug (Dart, 2009). As such, an effective post-marketing surveillance system for prescription drug would be one that provides specific information that was accurate, accessible and geographically specific. The FDA had put forward a

memo stating that all products containing high level of opioid drugs should be subjected to aggressive surveillance and risk management (Dart, 2009).

Criticisms of Pharmacovigilance Systems

Throughout the years, the FDA as well as the whole system of post-marketing surveillance received heavy criticisms (Furberg, Levin, Gross, Shapiro, & Strom, 2006; Lenzer, 2004; Mitka, 2006; Ray & Stein, 2006; Strom, 2006). Critics heavily denounced FDA for being limited and ineffective because it only used restricted number of data sources such as clinical trials and spontaneous reports to determine the safety of the drugs. Moreover, the FDA was criticized as not having legitimate control for carrying out and completing post-marketing safety studies (van Grootheest & Richesson, 2012, p. 371). According to Furberg et al. (2006), the FDA needed serious changes because the initial preapproval studies were designed in a way that prevented serious adverse events from detection. Moreover, massive underreporting of adverse events to the FDA post-marketing surveillance system made FDA assessments of risks inaccurate. The FDA was unable to go after the sponsors and manufacturers who did not fulfill or ignore their post-marketing safety study obligations. Lastly, the FDA was perceived as becoming more closely linked to the regulated pharmaceutical industry and weak when it came to their oversight abilities.

Moreover, most post-marketing study commitments that had been planned were never carried out. From 1970 to 1984, around 38% of post-marketing safety studies were not completed (van Grootheest & Richesson, 2012). However, even though this was the case, the FDA did not have the authority to take direct legal action against these

companies who did not follow through with their commitments (van Grootheest & Richesson, 2012). The FDA was said to have become too close to the industry it was supposed to be regulating. The critics claimed that regulatory duties of the institution should be separated from its post-marketing surveillance activities (van Grootheest & Richesson, 2012). The FDA reacted to this criticism by asking the IOM to evaluate the US drug safety system. As such, in September of 2006, the IOM produced a report that claimed the FDA should monitor the safety of a drug during its whole life cycle or should follow the life cycle approach. By following this approach, the FDA should determine safety signals, design studies that would confirm these signals, assess both the benefits and risks of drugs, and utilize risk-benefit assessments to integrate study results and disclose the main findings to patients and physicians (Psaty & Burke, 2006)

FDA's Adverse Event Reporting System

According to Hoffman, Overstreet and Doraiswamy (2013), more than 770,000 injuries or deaths annually could be attributed to adverse events linked to drugs already approved by the FDA. It had been estimated that around 28% of these adverse events could have been prevented if there was an effective computerized monitoring system in place. The FDA currently had a database of these drug-related adverse events, which was the FAERS as well as an adverse event database for medical devices, was called Manufacturer and User Facility Device Experience (MAUDE).

The FAERS was a database that consisted of information on the reports received by FDA containing information of adverse events and medication errors. The database was designed to supplement the body's post-marketing safety surveillance of drugs and

biological products. The FAERS abided with the international safety reporting guidance provided by the International Conference on Harmonization (Sakaeda, Tamon, Kadoyama, & Okudo, 2013).

This system acted as the post-market monitoring system for the FDA, which used historical data or information to supervise new adverse events and medication errors from drug and therapeutic biologic products (FDA, 2012d). This was designed to control the medical treatment and drug related issues that might lead to hazardous effects to the patients and consumer. The idea of recording and creating a computerized information database started due to the number of adverse events in the United States that was claimed to be 1 million every year, of which 44,000 to 98,000 was claimed had ended as fatalities (Leape, 2002).

At present, FAERS was considered the largest database of spontaneously reported adverse events and medication errors worldwide (Moore, Cohen & Furberg, 2007). At present, this database already contained 4 million reports of these adverse events. The FDA distributed the data under this system to the public and the public access enabled the researchers or experts to conduct pharmacoepidemiological or pharmacovigilance studies (Sakaeda et al., 2013).

The FAERS database had been utilized for analyzing the safety profiles of many different drugs. In addition, the highly suspicious drugs linked to serious adverse events were found by using the FAERS database, examples of which were the torsades de pointes (Poluzzi, Raschi, Motola, Moretti, & De Ponti, 2010). “Torsade de pointes is a form of polymorphic ventricular tachycardia occurring in a setting of prolonged QT

interval on surface electrocardiogram" (Gowda, et al., 2004, p.1). Through a larger number of reliable reports, the FAERS database, as well as other databases for reporting could lead to optimized pharmacotherapy (Sakaeda et al., 2013).

The FAERS had its advantages and limitations. The system did not necessarily have known disadvantages yet, but rather limitation in terms of the design. Despite the benefits of the system, it had its limitations, similar to other systems. The main limitation of the current FAERS was that the reports submitted to the FDA and integrated into the system lacked the comprehensive details of the consumers who experienced the adverse events or medication errors due to underreporting, differential reporting as well as uneven quality (Berlin, Glasser, & Ellenberg, 2008; Hochberg, Pearson, O'Hara, & Reisinger, 2009).

In general, adverse events were still underreported even with the emergence of spontaneous reporting systems (Figueiras, Herdeiro, Polonia, & Gestal-Otero, 2006; Hazell & Shakir, 2006; Lopez-Gonzales, Herdeiro, & Figueiras, 2009). While the rate of reporting might depend on the specific adverse event, the average rate of reporting was just 6% based on 37 studies (Hazell & Shakir, 2006). Various factors could explain why many adverse events were still not being reported, but the most critical one concerns the knowledge and attitude of health professionals (Lopez-Gonzales et al., 2009). Moreover, an educational intervention had shown to be the key to improve the rate of reporting (Figueiras et al., 2006). Through a patient-targeted survey, it was determined that 87% of patients relied on their physicians to establish if there was a possible connection between the adverse event and the use of statins; however, it was found that physicians had the

higher tendency to say no to the possibility rather than affirm the link (Golomb & McGraw, 2007). In addition, increased publicity and patient education for the FAERS were also important to encourage patient reporting (Du, Goldsmith, Aikin, Encinosa & Nardinelli, 2012). Currently, while the report rate had improved with the implementation of the FAERS (Rodriguez, Staffa & Graham, 2011), it was still not ideal to use the FAERS database in estimating incidence report rates because of the lack of a denominator, which signified the population size to determine utilization together with the number of times it occurred.

According to the FDA (2012a), adverse events and medication errors that had been made by healthcare professionals or experienced by consumers were not strictly mandated to be reported, reporting was voluntary in the United States. The adverse event and medication error reports were sent to the FDA by the consumers or end-users (for example, physicians, pharmacists, nurses, and other healthcare professionals) (FDA, 2012a). More so, these said individuals who had first or second-hand experience of the adverse events or medication errors might directly contact the products' manufacturers to report the problem. The FDA expected to receive the complaint report from the manufacturer filed by the consumers or healthcare professionals, as this process was to be done as it was stipulated in the regulations. All reports were then integrated in the FAERS, after which it was directly sent to the FDA or reported to the manufacturers (FDA, 2012a).

According to Hoffman et al. (2013), FAERS had the ability to acquire 700,000 reported adverse events annually across different therapeutic categories, making it a

powerful database. The database was widely used by many regulatory agencies and the pharmaceutical industry to look for data regarding drug safety. However, Hoffman et al. (2013) raised the problems with FAERS, such as the issue of complexity and costliness of proprietary data mining and signaling tools utilized by the regulatory agencies and major pharmaceutical companies. In addition, only those familiar with relational databases could obtain publicly available FAERS information, which limits the use of this database. This was why; the FAERS database was still currently mostly inaccessible to majority of physicians, pharmacists and consumers.

In addition, FAERS also suffered from limitations such as duplicate reporting, masking, amplifications, and insufficient information (Hoffman et al., 2013). The data on the FAERS might not be reliable because physicians might disproportionately report effects linked to newer drugs, even though other influence of other prescribed drugs and other factors might be the real cause of the adverse events. Data might also be questionable because physicians might have been influenced by publicity and marketing conditions. The lack of true incidence rates as well as accurate usage data could make the data in the FAERS unreliable (Hoffman et al., 2013).

Sentinel Initiative

To develop and implement the Sentinel System, the FDA performed pilot programs to aid in the forming of scientific methodologies, identifying data infrastructure needs, and enlightening the agency on how to establish strong data governance to form an accurate governance structure to ensure data privacy and security (Robb et al., 2012). During these earlier periods of development and implementation, the FDA discovered

that a distributed data system model involving voluntary participants was the key approach that could be used for coming up with an active safety surveillance system. Through this surveillance model, the FDA could make sure that data would stay in its local environment, unlike to a centralized approach, which would entail the consolidation of all data into one physical location (Robb et al., 2012).

The Mini-Sentinel pilot project was comprised of 20 organizations, led by the Harvard Pilgrim Health Care Institute (HPHCI) (Robb et al., 2012). The Mini-Sentinel program was a pilot under the FDA Sentinel initiative, as an effort to implement a national system that would assess the safety of medical products. The Mini-Sentinel was focused on signal refinement, or the improvement in the process of the assessing the magnitude of suspected links between specific medical products and specific adverse health outcomes (Robb et al., 2012). The FDA selected the particular product-outcome pairs, as it was the body most knowledgeable of the product. Under this program, the FDA differentiates between signal generation, signal refinement as well as signal evaluation (Robb et al., 2012). Signal generation involved the carrying out of statistical methods to discover possible safety signals among the pairs of non-pre-specified medical products and specific adverse outcomes. On the other hand, the process of signal refinement involved the identification of possible safety signal to establish more clearly whether evidence existed to provide a basis for the particular product-outcome pairs. Lastly, signal evaluation involved the attempts to assess the causal links between specific medical products and adverse outcomes by conducing epidemiological analysis (Robb et al., 2012). The Mini-Sentinel did not engage in data mining or other signal generation

operations as part of its standard practice. However, these activities were still included in the Mini-Sentinel Post-Licensure Rapid Immunization Safety Monitoring or PRISM program that was already exploring this capability in federal vaccine monitoring activities (Nguyen, Ball, Midthun & Lieu, 2012). The ongoing Mini-Sentinel hoped to be able to do the whole spectrum of surveillance activities, or in other words, it was able to carry out signal generation, to signal refinement and then to signal evaluation activities.

The collaborators behind the pilot project had worked since 2011 to assess some of the important issues for forming active medical product surveillance system in the United States (Robb et al., 2012). This included the best statistical and epidemiological approaches to use and what data and infrastructure were necessary for accurate surveillance investigations. The collaborators also assessed what kind of governance structure would have to be in place to support the initiative. Mini-Sentinel had been successful in serving as a general-purpose vaccine safety monitoring system (Robb et al., 2012).

Platt et al. (2012) assessed the Mini-Sentinel program, which designed different methods, tools, resources, policies, and procedures that could be used for the collection, analysis, and surveillance of electronic healthcare data. The data collected encompassed drugs, biologics, as well as medical tools (Platt et al., 2012).

Within two years of its existence, the Mini-Sentinel program had 31 academic and private organizations associated with it (Platt et al., 2012). Platt et al. (2012) found that the Mini-Sentinel program employed various activities such as the robust surveillance of a wide range of drugs and vaccines, as well as the improving of the common data model

to secure additional types of data. The data were sourced from different electronic health records and registries. The Mini-Sentinel program also had the ability to form or design new methodological capabilities and provided an approach to identifying and verifying additional and relevant health outcomes (Platt et al., 2012).

According to Forrow et al. (2012), the Mini-Sentinel Program was remarkable because it had its own organizational structure as well as principles that regulated its operations. These policies and structures allowed it to influence the structure and purpose of the Sentinel System (Forrow et al., 2012). The Mini-Sentinel program was also committed to the goal of the Sentinel Initiative, which was to ensure drug safety by regulating the ADRs of drugs already marketed to the public (Forrow et al., 2012). The program abided by the principles and regulations that uphold fair information practices (Forrow et al., 2012). As such, the privacy of individuals and the confidentiality of healthcare data were observed. Still, the success of this initiative still remained largely upon the users' satisfaction (Forrow et al., 2012).

Effects of Pharmacovigilance

According to Behrman et al. (2011), the FDA Sentinel Initiative served as an additional tool for the FDA to evaluate the safety of medical products, and more importantly, acted as a national resource for the FDA to take advantage of investigating medical product performance. Moreover, the Sentinel Initiative became an early working model for secondary uses of data, and a national resource of a learning healthcare system. Robb et al. (2012) explained that the FDA Sentinel Initiative was borne from responses to the congressional mandate in Section 905 of the FDA Amendments Act of 2007. This

initiative was intended to provide advantage to existing healthcare information to allow the FDA to perform active post-market safety surveillance in support of the current surveillance systems it had (Robb et al., 2012).

According to Robb et al. (2012), the idea of secondary use, or utilizing data collected for other intentions, such as electronic health record data initially recorded for patient care or insurance claims data utilized for reimbursement was not a new one. Nonetheless, due to the expansion of the availability of these types of data, based on the passing of the US Health Information Technology for Economic and Clinical Health (HITECH) Act, more attention had been given to the leveraging of these data for purposes they were not intended for, such as updating the public on specific health issues. One of these issues was the safety surveillance of medical products (Robb et al., 2012). The FDA, through the use of various administrative and claims databases, as well as electronic health record systems and registries, would now have the ability to scrutinize regulated medical products nearly as fast as real time and to better comprehend product safety (Robb et al., 2012).

According to Robb et al. (2012), the system being designed and developed under the auspices of the Sentinel Initiative would be able to aid the FDA in discovering and analyzing post-market safety signals through signal generation, signal refinement, and signal evaluation, which referred to the concern over an excess of irregular and negative events when compared to what was traditionally associated with a product's use. Signal refinement specifically allowed the FDA to assess a drug at various times during its life cycle (Robb et al., 2012). Should a drug be assessed to lead to adverse outcomes, the

FDA might conduct additional assessments to validate the signals it received. The validation process was performed to ensure that the adverse outcome from the drug was not spurious (Robb et al., 2012). Overall, the Sentinel Initiative was helpful to the FDA when making regulatory decisions.

Summary

The current FDA consumer safety surveillance system used the FAERS, which had limitations, including not allowing real time data collection. In response to these limitations, the FDA launched the Sentinel Initiative in 2008 (Platt et al., 2012). This study provided a comparative case study between the two systems, investigating the influence of the Sentinel Initiative on users of FAERS.

The review of literature outlined the existing knowledge pertinent to this study. It illuminated the need for ADR reporting systems and their benefits. It also specifically covered the Sentinel Initiative and the Mini-Sentinel Program, which were the programs of interest for the proposed study.

The next section covered the methodology used in carrying out the proposed study, which was approved by Walden IRB committee. The study implemented a comparative case study design, which was qualitative in nature. Survey questionnaires used to determine the perceptions of the participants regarding the costs and benefits of the Sentinel Initiative compared with the current FAERS surveillance methodology. The data analysis technique that used was content analysis, which involved the development of thematic categories and themes from qualitative data.

Chapter 3: Research Methodology

The purpose of the comparative case study of the current FAERS surveillance system and the new FDA Sentinel Initiative was to determine the potential impact and benefits of the Sentinel Initiative in terms of consumer safety. Currently, the reporting system used by the FAERS was voluntary and quarterly, and data was entered from the point of care (Powers & Cook, 2012). Instead of depending on point-of-care data collection, the Sentinel Initiative had access to multiple existing data systems such as electronic health record systems and medical claims databases in real time (Platt et al., 2009).

This was a qualitative study was focused on the perceptions of individuals who had worked closely with the FAERS program and were familiar with the Sentinel Initiative. As such, no quantification of data waswas carried out to compare information on the two programs. Instead, the responses of participants regarding their perceptions was used to illustrate differences between the two programs. In this study, the two cases referred to the perceptions of the FAERS and perceptions of the Sentinel Initiative. This chapter presents details of the design, sampling and sampling methodology, data collection methodology, and data analysis.

Research Design and Rationale

In general, qualitative studies were different from quantitative studies in the sense that qualitative studies permit the study of a particular phenomenon in depth within the participants' natural settings (Denzin & Lincoln, 2005). Qualitative research is advantageous due to the richness of data gathered especially when data gathering was

performed through interviews, which allowed interviewees to expound on their answers without being limited by the predetermined choices for answers or the need to write down answers to questions (Moriarty et al., 2011). Qualitative designs were beneficial when existing research in an area was limited. Moreover, given the limitations of time, qualitative data was considered appropriate for this study.

Case studies were qualitative methods that allowed for in-depth and multifaceted explorations to generate rich knowledge about a given subject (Crowe et al., 2011). According to Zainal (2007), case study enabled the researcher to explore and understand complicated issues. Case study research could be considered a robust approach for understanding issues holistically and deeply (Zainal, 2007). Researchers who used a case study method could closely analyze the data gathered within a specific context (Zainal, 2007). The method was also appropriate for studies with a small geographical area or a very limited number of participants. It was also the best method for investigating real-life issues because it allowed for a detailed contextual analysis of a small number of events as well as conditions and their relationships to each other (Zainal, 2007).

According to Zainal (2007), case studies had various advantages. Case study research allowed for examination of data within the situation in which the activity happened. Moreover, the case study method allowed the researcher to explore or characterize the data within real-life contexts as well as explained the complexities associated with the real-life issues that survey research or experimental methods could not capture (Zainal, 2007). When multiple cases were examined and compared, then it was called a comparative case study (Abadie, Diamond, & Hainmueller, 2010). In this

study, the first case was the perceptions of the old system and the second case was the perceptions of the new system.

Methodology

Population

The target population included safety professionals from drug companies who had self-reported knowledge or expertise in assessing consumer impact. The participants were selected from various departments within pharmaceutical companies and across geographical locations. The participants were subject matter experts in the field of pharmacovigilance.

Sample and Sampling Procedures

Samplingincluded participants at different levels from different therapeutic departments such as pain and inflammation, cardiovascular, and psychiatric and mental health. The geographical locations included selected pharmaceutical companies in the United States. The participants were(a) had worked closely with the current FAERS surveillance system and were familiar with the FDA's Sentinel Initiative and (b)were from prominent pharmaceutical companies involved in the programs of focus in this study. Criteria confirmation waswas performed by asking participants questions that conformed to the criteria for inclusion during the time the interview was to be scheduled.

Mason (2010) stated that the required sample size for qualitative studies could be determined based on the point of data saturation. Saturation indicated that the data gathered had reached consensus, and using more resources by recruiting more participants would result in marginal increases in new data (Mason 2010). Yin (2003)

posited that qualitative case studies usually had small sample sizes as opposed to quantitative methodology, which normally relied on larger sample sizes. Polkinghorne (2005) stated that qualitative data were collected in the form of written or verbal language, and the sample size was not the primary focus. In addition, Patton (2005) stated that there were no specific standards for sample size in qualitative studies, and that, "sample size depends on what you want to know, the purpose of the inquiry, what's at stake, what will be useful, what will have credibility, and what can be done with available time and resources" (p. 244). However, a sample size of 10-20 participants was usually considered sufficient to achieve data saturation because a review had shown that the small sample size could facilitate gathering enough detailed accounts of personal experiences to arrive at a consensus among answers (Mason, 2010). Hence, 20 participants who had worked closely with the FAERS program and were familiar with the Sentinel Initiative were recruited for this study.

For sampling methodology, purposive sampling was used with the snowball technique for more efficient recruitment of participants. According to Latham (2007), purposive sampling referred to choosing a sample based on the researcher's knowledge of the population and its elements and matching these elements to the nature of the research aims. As such, the population was not randomly selected. Instead, they were chosen because they could answer the questions regarding a specific matter or product. This method was best for research studies that included subjects who are part of a larger population that were easily identified but enumerating them all was impossible (Latham, 2007). In addition to purposive sampling, snowball sampling was another sampling

technique used. Snowball sampling took advantage of social ties and network referrals of potential participants who possessed the characteristics for inclusion in the study (Latham, 2007). According to Latham (2007), this would include the researcher depending on previously identified subjects to identify others who had similar characteristics. To recruit samples using purposeful sampling with snowball sampling, the participants were sought within pharmaceutical companies in the United States who were selected because of their involvement with the FAERS program. Participants were only those who met the inclusion criteria of having worked with the FAERS and were familiar with the new Sentinel Initiative. The nature of the study was discussed with the participants. The contacted participants referred the study to other individuals who fit the inclusion criteria. The prospective participants were contacted through formal invitation letters.

An informed consent form (Appendix B) was attached with the formal invitation letter (Appendix A) sent to potential participants. The informed consent form included a brief description of the study, the purpose, and the role of the participants. Participants were also informed that their interviews would be recorded. Once the potential participants agreed, they signed the informed consent to signify their acceptance of involvement in the study. After signing the informed consent, the participants brought the forms to the interview; unsigned forms were also available during the interview for participants who had forgotten to bring their signed forms. The participants were contacted via telephone or email to arrange a convenient date and time for the telephone interview. Telephone interview was more convenient because of geographical distance

and reduced the travel burden for the participants. Specifically, each participants' was asked for his or her consent prior to the beginning of the telephone interview. The telephone interview lasted approximately 45 minutes. Participants who preferred the telephone interview faxed or emailed the copies of their informed consent with their signatures.

Data Collection

Data collection was facilitated with the use of semi-structured interviews. Prior to the interview, the participants were reminded of the content of the informed consent. They were also reminded that participation was voluntary, that their identity would be kept confidential, that the interview would be recorded, and that all files and notes would be kept secured inside a locked cabinet in a private office and would be destroyed after 5 years from the completion of the study.

To facilitate the semi-structured interviews, an interview guide was used that contained questions that were focused on gathering answers that were in line with the purpose of the study. To make sure that the participants could easily and accurately understand the questions in the interview guide (Appendix C), a pilot study was conducted for comprehensibility. In the pilot study, five participants were recruited with the same qualifications to participate in the interview (from the pharmaceutical companies selected for this study). These pilot study participants interpreted each question and discussed their feedback during a one-on-one session after the completion of the interview. Notes were taken of the feedback and no change in the interview guide was required after the pilot study was completed. At the end of the interview, the participants

were thanked. The participants were given an opportunity to ask questions and request clarifications, which were addressed.

Though the interviews were expected to last 45 minutes, there was no time limit as each interview was dependent upon the flow of the conversation between me and the respondent. The entire data collection process, which included the recruitment process, pilot study, and completion of the 20 interviews, lasted twelve weeks during Fall 2015.

Data Analysis Plan

To analyze the transcribed data, thematic content analysis was used. Content analysis led to the identification of important themes. Content analysis was "a research method for the subjective interpretation of the content of text data through the systematic classification process of coding and identifying themes or patterns" (Hsieh & Shannon, 2005, p. 1278). The thematic pieces were weaved together to form an integrated picture that was aligned with the research questions, which were as follows:

Research Question 1: What are the prospective benefits of the FDA's Sentinel Initiative as compared with the FAERS surveillance methodology?

Research Question 2: What are the challenges and negative impacts of the FDA's Sentinel Initiative as compared with the FAERS surveillance methodology?

Research Question 3: What are the lessons learned that can enhance the scope of the Sentinel Initiative?

According to Polit and Beck (2004), the researcher began the analysis of data by looking for themes, which involved looking for commonalities, natural variations, and patterns across the responses of the participants. To uncover themes for this study, the six

steps of Braun & Clarkes' (2006) thematic analysis were used as a guide, which consisted of the following:

1. Familiarization with the data: This involved transcribing, reading, and re-reading the audio-recorded interview data, and taking note of initial ideas. Final raw data was the transcripts for each of the interview sessions.
2. Codes generation: Code of interesting features of the data were developed in a systematic fashion as applied to the entire data set. The entire data set was coded based on the coding scheme developed.
3. Searching for themes: the codes were collated into potential themes by gathering all data relevant to each potential theme.
4. Theme review: The themes were checked in relation to the coded extracts and the entire data set. Through this step, a thematic map of the analysis was generated.
5. Theme definition: Themes represented the most cited codes within a category. Codes, categories, and themes were analyzed. These were defined accordingly based on the codes they contained. Codes represented the smallest unit of idea or information relevant to the study. Categories were composed of interrelated codes that pertained to a larger but similar idea.
6. Report generation: The final report of the data analysis was developed and selected vivid and compelling examples to further explain the findings. For each category, tables contained the codes that emerged from that category. Themes represented the recurrent ideas that emerged from the data.

All of the responses were read and analyzed; then extracted the significant statements that pertained directly to the issue. Following this, meanings for significant statements were formulated and categorized these into clusters, which were considered to be the themes. Following these steps, the findings were integrated into an exhaustive description. Then a comprehensive description of the phenomenon under study was formed.

Validity

The participants were recruited for the study. The semi-structured interviews with the 20 participants were conducted. It was ensured that the sessions were productive in eliciting useful information from the participants by following the proper techniques for one-on-one interviews. The interview guide was followed to ensure validity and reliability. It was ensured the study was not impacted by any bias to ensure that data was accurate and objective. To minimize bias, the study's credibility, dependability, and transferability was upheld. Below were the ways to ensure these respectively.

Credibility and Dependability

To ensure credibility, member checking were performed through verification of accuracy of conclusions with participants (Thomas & Magilvy, 2011). The researcher was as transparent as possible with the participants, by sharing the interpretations and conclusions with them. Member checking was performed to double check if the information transcribed and written corresponds to what the participants said (Thomas & Magilvy, 2011). Member checking was done by asking participants to review the transcript and solicit feedback regarding the transcript accuracy. To ensure dependability,

the researcher audiotaped interviews, with the consent of the participants, and later on, the researcher transcribed the interviews verbatim. An audit trail had been kept and used by the researcher where observations were recorded and made available for peer reviewers (Thomas & Magilvy, 2011). Pseudonyms, known to the researcher alone, were used to replace all these identifying information and transcript of a participant. For report generation, aggregate data was used; for instances that required the researcher to single out a particular data point, pseudonyms was used instead.

Transferability

Thomas and Magilvy (2011) claimed the association between transferability and external validity. Transferability involved the study's ability to transfer findings to another population different from the one used by the researcher of the original study (Thomas & Magilvy, 2011). All the data collected, audiotapes, and journal notes, and transcriptions were kept in their original form. This was done to allow easier access should there be a need to recreate the study in a different setting. The data did not contain any names. Pseudonyms, known to the researcher alone, were used to replace all these identifying information to ensure the confidentiality of the participants.

Ethical Procedures

Researchers needed to ensure that they recognized and protected the rights and general well-being of their participants (Resnik, 2010). Ethical lapses in research could harm human and animal subjects, students, and ultimately, the public (Resnik, 2010). Before participants actually took part in the study, they were asked to sign an informed consent containing the details of the study and the information they needed to know as

they partake in the study. The ethical issues covered by the informed consent were confidentiality and voluntary nature of participation. Upon agreeing, the participant was to sign the consent form as proof that they agreed to participate in the study.

Confidentiality was an important issue that must be addressed in using human participants in a research. To do this, any information was deleted that might identify the respondents in any way. Pseudonyms, known to the researcher alone, were used to replace all these identifying information. For report generation, aggregate data was used; for instances that required to single out a particular data point, pseudonyms was used instead. The participants were also informed that the interview would be recorded. After transcribing, each respondent could review the transcripts of their interviews for mistakes and make requests for removal of any undesirable word or phrase. This process was called member checking. According to Harper and Cole (2012), member checks were important to make sure that an authentic representation was made of what was expressed during the interview sessions.

Being a participant in the study was voluntary; and hence, they would or would not agree to sign the consent form. Voluntary participation also implied that there was no reward or consequence for being a participant of the study. Even if they had already consented to participate, participants still had the option of termination their participation of the study, without having any consequence on their part. They also had an option to choose not to answer any particular question, which they felt uncomfortable answering.

All files containing data related to the study, including all physical and electronic files like audio recording, interview transcripts, printed documents, and other notes, were

kept inside a locked cabinet located at a private office where I had access to these files. These files would be kept for five years after the entire study had been finished and completion of this dissertation. After five years, they would be destroyed through shredding or burning.

Summary

The purpose of this comparative case study of the current FAERS surveillance system and the new FDA's Sentinel Initiative was to determine the impacts and benefits of the Sentinel Initiative in terms of consumer safety. Currently, the reporting system utilized by the FAERS was voluntary and quarterly (Powers & Cook, 2012). Instead of depending on point of care data collection, the Sentinel Initiative would access multiple existing data systems such as electronic health record systems and medical claims databases (Platt , Wilson, Chan, Benner, Marchibroda, & McClellan, 2009).

This was a qualitative study focusing on the perceptions of individuals who worked closely with the FAERS program and were faimiliar with the new Sentinel Initiative. As such, no quantification of data was carried out to compare information on the two programs. Instead, the responses of participants regarding their perceptions were illustrated any differences between the two programs. This chapter showed that the research questions are in line with the purpose of the study, a comparative case study approach was chosen for this study. Semi-structured interviews were used to gather data for the study from 20 participants who worked with the FAERS program and familiar with the Sentinel Initiative. Participants were recruited using purposive sampling and

snowball sampling. To analyze data, content analysis was used. The next chapter will discuss the details of the data gathered for the study.

Chapter 4: Results

The purpose of this comparative case study of the current FAERS surveillance system and the new FDA's Sentinel Initiative was to determine the potential impact and benefits of the Sentinel Initiative in terms of consumer safety. Currently, the reporting system utilized by the FAERS is voluntary and quarterly, and data was entered from the point of care (Powers & Cook, 2012). Instead of depending on point-of-care data collection, the Sentinel Initiative had access to multiple existing data systems such as electronic health record systems and medical claims databases in real time (Platt et al., 2009). There were differences between the FAERS and the Sentinel Initiative that were identifiable by the pharmacovigilance experts.

The following were the research questions of this study:

RQ1. What are the prospective benefits of the FDA's Sentinel Initiative as compared with the FAERS surveillance methodology?

RQ2. What are the challenges and negative impacts of the FDA's Sentinel Initiative as compared with the FAERS surveillance methodology?

RQ3. What are the lessons learned that can enhance the scope of the Sentinel Initiative?

FAERS was known to be a useful tool for the FDA to ensure compliance with reporting regulations and responding to outside requests for information. The reports in FAERS were evaluated by the FDA and clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). The main goal of the FAERS surveillance system was to ensure the protection

and safety of the consuming public (FDA, 2016). The Sentinel System enabled FDA to actively query diverse automated health care data holders - like electronic health record systems, administrative and insurance claims databases, and registries - to evaluate possible medical product safety issues quickly and securely. The FDA Adverse Event Reporting System (FAERS) was a database that recorded the relevant information on adverse events of drugs or medication errors that were submitted to FDA (FDA, 2016).

The database of the FDA was designed to support the FDA's program for the safety surveillance of pharmaceutical medications for drug and therapeutic biologic products. FAERS captured data by either consumer reporting directly to drug manufacturers or by calling the FDA directly and which is why there was a limited set of information going to system. On the other hand, the FDA's Sentinel Initiative was a national electronic system that would allow the FDA to track the safety of medications, medical devices, and drugs upon reaching the market. The FDA was able to query consumers and examine the health record systems to ensure that drugs were safe for human consumption (FDA, 2016). The Sentinel System allowed the FDA to monitor the safety of drugs and medical products including devices with the assistance of many collaborating institutions throughout the United States. Data partners in this initiative included medical centers, health maintenance organizations (HMOs), and health care systems like hospitals (FDA, 2016).

Pilot Study

To facilitate the semi-structured interviews, an interview guide was used that contained questions focused on gathering answers that were in line with the purpose of

the study. To make sure that the participants could easily and accurately understood the questions in the interview guide; a pilot study was conducted for comprehensibility. Five participants were recruited with the same qualifications to participate in the interview (from the pharmaceutical companies selected for this study). These pilot study participants interpreted each question and discussed their feedback during a one-on-one session after the completion of the interview. At the end of the interview, the participants were thanked.

Five participants were recruited for the pilot study. The participants worked in pharmaceutical companies and had experience in the pharmacovigilance department. The participants were interviewed separately and their feedback was sought about the content of interview questions. No change in interview guide was required. Data collection was continued with other participants.

Setting

The participants included safety professionals from drug companies who had self-reported knowledge or expertise in assessing consumer impact. The participants were selected from various departments within pharmaceutical companies and across geographic locations. The participants were subject matter experts in the field of pharmacovigilance. The setting of the study emphasized the importance of reporting the adverse impacts of medication and drugs.

Summary of Demographic Information

The study included 20 interviewees who had different numbers of years of experience in the field of pharmacovigilance. All participants had worked in major

pharmaceutical companies and had previous experience in pharmacovigilance departments or were working in the departments at the time of the study. The participants were taken from different levels in their respective pharmaceutical companies, including junior level and senior levels positions. Some had full-time positions or some were consultants in pharmaceutical companies at the time of the study or in the past. Participants who were at junior levels had at least 2 years of experience, and others had five years of experience or more in the field of pharmacovigilance. Participant demographics are presented in Table 2.

Table 2

Demographics of the Interviewees

Interviewees	Experience (In Years)
1	2+
2	15+
3	25+
4	2+
5	25+
6	20+
7	12+
8	15+
9	10+
10	15+
11	5+
12	4+
13	20+
14	4+
15	10+
16	14+
17	2+
18	10+
19	16+
20	15+

Data Collection

Data collection was facilitated with the use of semi-structured interviews. Before each interview began, the participants were reminded of the content of the informed consent. They were also reminded that their participation was voluntary, that their identity would be kept confidential, that the interview would be recorded, and that all files and notes would be kept secured inside a locked cabinet in a private office. These files would be destroyed after 5 years from the completion of the study.

The semi-structured interviews were expected to last 45 minutes. However, the interviews had no time limit because each interview was highly dependent on the flow of the conversation between me and the respondent. The entire data collection process, included the recruitment process, pilot study, and completion of 20 interviews, lasted twelve weeks. Data saturation was met after interviewing 20 participants in answering the research questions of the study.

Data Analysis

The data analysis used was cross-case analysis, a method of research that allowed the mobilization of knowledge from several case studies (Khan & VanWynsberghe, 2008). The cross-case analysis allowed for comparison of similarities and differences in the outcome based on the interviews conducted (Maben & Penfold, 2015).

Provisional deductive codes were identified from the predetermined input, output, and expected outcome of the two programs. These deductive codes helped in identifying relevant inductive information concerning the program. The five deductive codes included the following: (a) data collection, (b) use of health data, (c) active system, (d)

voluntary reporting, and (e) systematic database. From these codes, 29 codes were identified covering five interview questions responded by 20 participants. Eighty pages of transcripts were read and the codes were sorted, which are presented in Appendix D.

The 29 codes that emerged from the collected data were data collection, use of health data, active system, voluntary reporting, systematic database, privacy, relative assessment, unexpected adverse effects, threats to public health, health safety, patient-centeredness, coincidental occurrences, risk evaluation, reporting model, post-drug approval activities, evaluation of products, responsibility, accountability, preventive action, alerting the public, evidence-based, vigilance, accessibility, inclusive, discovery of new risks, other stakeholders, drug safety, opportunity to improve healthcare professionals, and disease occurrence. For each emerging code, a meaning was determined based on the verbatim provided by one or more participants.

For the data collection code, it was determined that FAERS and Sentinel collect data from patients regarding the adverse effects of drugs. The sample quote from participant 17 was:

> The availability of vast volume of data which includes not only the drug reaction details but also the information such as medical history of the patient, personal details such as age etc. also all this information will help us derive relevant and durable information from the data.

For the use of health data code, it was determined that health data is used for the record of FDA. The sample quote from Participant 14 was, “There are various organizations and to be exact I believe 18 organizations that are involved in retrieving health data.” The Sentinel Initiative is an active system of reporting was determined for the active system code. Participant 14 responded, “So benefits like I told you that it's an

active system they have immediate results." Participant 1 responded, "FAERS is basically everything is voluntarily done most of the time it is more specific to particular patients." For the voluntary reporting code, it was determined that the voluntariness of reporting is evident in the regulation. For systematic database, Participant 7 stated, "FAERS is the FDA adverse events reporting system. It's a database that contains the information on Adverse events (AE's) and medication errors" and it was determined that the reporting the ADRs allow having a systematic database. Participant 6 stated, "I really see here is the privacy issue- The HIPAA compliance. I don't know if the patients would like to share their information to a third party", which resulted in a privacy code. It was determined that privacy of the individuals who report adverse effects might be at stake. Similarly for relative assessment code, it was determined that there can be differences in how a person assesses or evaluates the effects of drugs. For the relative assessment code, it was determined that there can be differences in how a person assesses or evaluates the effects of drugs. Participant 8 responded:

> With the FAERS system addressing adverse differential FAERS is dependent on whether the patient really calls FDA or health care company and that one is limited. Whereas with Sentinel the patient may be either talking to healthcare profession that I had reaction with drug and it might get reported much more better than the FAERS system where the patient might even not know where to report.

For the unexpected adverse effects code, it was determined that the unexpected adverse effects of drugs should be reported in order to be prevented. Participant 12 responded, "There would be more clinical information available regarding the adverse effect and what was happening so that would be one major benefit". Participant 2 mentioned, "I say society it means all the players who are responsible for managing healthcare in the

system." It was determined that the adverse effects of drugs pose threats to public health which led to the threats to public health code. Health safety of patients can be achieved if drugs are safe was determined for the health safety code as Participant 2 stated, "The potential benefits of the patients ultimately the FDA was created to benefit the patients and consumers and the larger population will be benefited by this and more genotyping and genomics data." For the patient-centeredness code, it was determined FAERS and Sentinel Initiative are focused on the welfare of patients. Participant 20 stated:

> I think it's mostly patients safety, they are having a lot of information sharing it they are able to share it, they are compiling they are getting a great deal more info on all these products hopefully to be used for a patient safety.

Coincidental occurrences on patients that do not have direct correlation to the drugs might be mistaken as adverse drug effects that were determined for the coincidental occurrences code. Participant 2 stated:

> I can confirm it if you like all the adverse reactions that happened whether it was on doctors clinic or it happened anywhere else in the hospital only 6-10% were reported since the institution established FAERS whereas the sentinel program because it is not asking you report anything it is asking you to just keep your data in a particular format.

For the risk evaluation code, it was determined that the risks on drugs will properly be assessed if there is a proper reporting model. Participant 13 stated:

> I think the challenges are that you know with a lot of data you also comes with it is noise and you know the quality of data and probably you can have where signals will get lost and then you have different interpretations of signals of what is actually a risk and what is I think it gets a little bit murky with that large amount of data.

The reporting model of how adverse drug effects are recorded should be systematic is determined for the reporting model code. Participant 5 stated, "It doesn't seem that they

have a separate method they can use to overcome under reporting of worst events so if the data is not there they can obtain any additional information." Post-drug approval activities must be evaluated to ensure the safety of the public was determined for the post-drug approval activities code. Participant 4 stated:

> So basically they use all these query methods so that they can query these large database to determine to get the desired results of what are on what features are they looking for and what kind of problems they want to solve or especially what drug they want to improve.

The proper evaluation of products should be the priority in order to ensure health safety was determined for the evaluation of products code. Participant 18 stated, "Evaluation is done principally by FDA and they will be the one who will analyze the data and gather critical information out of this." For the responsibility code, it was determined that there should be a government agency that regulates drugs in order to monitor responsibility on the safety of drugs. Participant 20 stated, "So here again I think the agency has the ultimate responsibility when it comes to reporting though in general it is on … it's on the health care professionals and consumers."

For the accountability code, it was determined that there should be a government agency that regulates drugs in order to monitor accountability on the safety of drugs. Participant 17 stated, "Again the FDA, the stakeholders are solely responsible for implementing and evaluating these methods." Participant 13 stated, "I think there are may be 18 organizations collecting this data help data warehousing and ensure companies like that have access to vast of data and vast of health data." The reporting model is a form of preventive action to ensure that future similar incidents will be prevented which was determined for the preventive action. For the alerting the public code, it was determined

that the public has the right to know on the possible adverse drug effects based on the experience. Participant 17 stated:

> The potential challenges which I am looking upon in this under reporting of adverse from these methods is to instill a sense of security amongst the patients and we have to educate them that their personal data is only used for medicinal and research purposes. The meaning for evidence-based code was determined as the reporting of adverse drug effects by the patients will allow evidence-based conclusions.

Participant 19 stated, "Doctor must have prescribed something and there must be some evidence and records they don't have to wait for many years." Vigilance in the pharmaceutical industry must be improved was determined for the vigilance code. Participant 16 stated, "I mean all the stake holders that are involved should be responsible whether be the manufacturers or the distributors or the FDA or the healthcare professionals or even the patient." For the accessibility code, it was determined that the records and data collected should be made accessible to the public. Participant 16 also stated, "Information is generally documented within the healthcare providers database it's more readily accessible to FDA to perform to better evaluate the data." For the inclusive code, it was determined that a more inclusive system should be created so that the development will go beyond research purposes. Participant 5 responded, "To obtain extensive stakeholders and partners to participate in this imitative there will have to some kind of method to educate consumer for this work so that they may be able to share their health care info to the database." It was determined that new risks on the adverse drug effects will be prevented for discover of the new risks code. Participant 4 stated:

> That it can eliminate under reporting to extent but it will be still be there because the access to data is small and I think they are also working on it once data bases

> are linked and they have access to those databases then they will have better analysis to problems of adverse drug reactions.

Participant 5 stated, "Consumer may not allow releasing their health care info and they need to increase their stakeholders if they want to expand and implement all over the country." It was determined that a more inclusive progress in the field of pharmacovigilance is possible if there are more stakeholders that led to the other stakeholder's code. For the drug safety code, it was determined that drug safety should be prioritized in ensuring that there are proper reportorial mechanisms. Participant 17 stated, "It will help derive the FDA and to evaluate about a drug and take some safety measures about a drug." For the opportunity to improve healthcare professionals code, it was determined that healthcare professionals will improve their performance if the drugs are properly regulated. Participant 5 stated, "So the challenge again would be the lack of partnership, they have to increase their partnership to all physicians, pharmacies in order to expand their data base." Lastly for the disease occurrence code, it was determined that disease occurrence can be lessened if there is proper regulation of drugs available in the market. Participant 19 stated, "There are some other diseases and other things that I have and if I am going to take this medication it going to have an impact on me."

As codes emerged in the transcripts, I reviewed and categorized these codes for further analysis. Out of the 29 codes, I identified six categories. These were: data collection, patient's health, regulatory mechanism, preventive measure, other stakeholders, and drug manufacture. For the first category, the associated codes for data collection were data collection, use of health data, active system, voluntary reporting, systematic database, privacy, and relative assessment. The meaning was determined

based on associated codes derived from participant's response. The meaning from first category was determined as FAERS and Sentinel Initiative provide a systematic data collection for a database that would use health data to improve public health. For the second category, the associated codes for patient's health were unexpected adverse effects, threats to public health, health safety, patient-centeredness, and coincidental occurrences. The meaning from second category was determined as the adverse effects of drugs will be recognized and the safety of the patients and the public will be prioritized.

For the third category, the associated codes for regulatory mechanism were risk evaluation, reporting model, post-drug approval activities, and evaluation of product responsibility and Accountability. The meaning was determined as the reporting model provides a regulatory mechanism after the drug approval activities in order to evaluate the medicinal products. For the fourth category, the codes for preventive measure were preventive action, alerting the public, and evidence-based vigilance. The meaning derived from this category and associated event was the presence of FAERS and Sentinel Initiative improves the vigilance of the public towards the adverse effects of drugs. The fifth category, other stakeholder were based on codes such as accessibility, inclusive, discovery of new risks, and other stakeholders. The meaning determined from these codes and category was a more inclusive database will include other stakeholders and make the records more accessible. The sixth category was drug manufacture which was based on codes such as drug safety, opportunity to improve health care professionals, and disease occurrence. The meaning derived from these codes and category was the

availability of a surveillance system such as FAERS and Sentinel Initiative will improve drug safety.

Themes were derived from analyzing the responses of the participants in the interviews. Each interview was thoroughly read and analyzed. The codes were created based upon analyzing each interview session. The cross-case analysis was conducted by analyzing the codes derived per interviewee. Twenty nine codes were derived and these codes were divided into six categories. These themes are further discussed in the latter part of the chapter.

Evidence of Trustworthiness

The results of the study were credible and dependable. The interviews verbatim were transcribed so as not to avoid misinterpretation or poor recall of the answers provided by the participants. It was also confirmed from the audio whenever there were ambiguous content within the transcripts of the interview. To ensure dependability, it was ensured an audit trail that was available for peers to review. The names of the participants were maintained confidential. This improved that trustworthiness of the study, because revealing the identities of the participants might hamper their intent to be open and prudent in providing the information for the research. The transcripts used for the study were faithful to the original interviews conducted with the participants.

Thomas and Magilvy (2011) claimed the association between transferability and external validity. Transferability involved the study's ability to transfer findings to another population different from the one used by the researcher of the original study (Thomas & Magilvy, 2011). Hospitals could benefit from the study and ensured that

ADRs were reported. The demographic profile of the interviewees indicated that the study would have similar results when a different set of pharmacovigilance experts were interviewed. The external validity of the study was ensured by the strict scrutiny of the data collected from the interview. To ensure transferability of the study, the audio files were promptly recorded of the interview and the verbatim transcript. Pseudonyms, known to the researcher alone were used to replace all these identifying information to ensure the confidentiality of the participants. The snowballing techniques were utilized and I met different people who worked in pharmacovigilance department. The participants who agreed to participate in the study had self-reported knowledge of Sentinel initiative. These participants worked closely in drug safety department of pharmaceutical companies. Hence, they had work closely with FAERS.

Results

Based on the analysis of the codes and categories, theme 1 emerged, “The presence of FAERS and Sentinel Initiative improves the vigilance of the public towards the adverse effects of drugs and promotes health and public safety.” This theme was reflected from the following categories: Patient's health; preventive measure; drug manufacture; and, other stakeholders. The first theme was derived from 52 responses. For this theme, 52 was the sum of the total responses from the codes where this theme emerged from. The second theme showed that, “FAERS and Sentinel Initiative provide a systematic data collection for a database that would use health data to improve public health.” This theme was reflected from the category of data collection and gathered 28 responses. For this theme, 28 responses was the total of the responses to the codes where

this theme emerged from. The third theme showed that, "The reporting model provides a regulatory mechanism after the drug approval activities in order to evaluate the medicinal products." This theme was attained from 22 responses. To summarize, the following were the themes of the study:

Theme 1. The FAERS and Sentinel Initiative improve the vigilance of the public towards the adverse effects of drugs and promote health and public safety.

Theme 2. FAERS and Sentinel Initiative provide systematic data collection for a database that would use health data to improve public health.

Theme 3. The reporting model provides a regulatory mechanism after the drug approval activities in order to evaluate the medicinal products.

The three themes will be further discussed below and codes and categories associated with the themes can be found in Appendix E. More comprehensive information on the responses of the participants was shown in Appendix D (Emerging Codes and Categories).

Theme 1. The presence of FAERS and Sentinel Initiative improves the vigilance of the public towards the adverse effects of drugs and promotes health and public safety.

Patient's Health. The maintenance of patient's health was the priority in every surveillance mechanism that promoted the monitoring of the adverse effects of drugs. There were some instances where the performance in pharmacovigilance could be improved from the current set up of FDA's Sentinel. There was a possibility of tracking

back the results and effects of a certain drug and medication so that it could be comprehensively studied and researched on. As suggested by Participant 15:

> See the benefits can be really big and the reason why I say that if you look at the data reporting this not even ten years back I would suggest 5 years back for every year you see there are so many challenges and the changes that we are coming across in lifestyle and day to day activities which leads somewhere towards the pharmaceutical companies and that is where they are able to do all this new medications and launch all these drugs but at the same time behind the scenes somewhere cumulative data is helping them to take the proactive initiative.

The awareness of the people and the patients should be improved in order to increase the effectiveness of the Sentinel surveillance system. With the awareness that data could be accessed to inquire about certain information on the effects of medication, the patients would become proactive in interacting with the doctors. The patients would be more informed with the advice that they derive from their physicians. As observed by Participant 4:

> So like I told you earlier people were not aware about these portals and reporting of various drug problem since it's a common interaction between the doctor and the patient so its take care of the under reporting and all these database are linked in sentinel so they will have access to data in terms of determining what all adverse reaction can be caused by a drug.

Unexpected adverse effects. The unexpected adverse effects of drugs should be reported in order to be prevented. Quoting Participant 12, "There would be more clinical information available regarding the adverse effect and what was happening so that would be one major benefit." According to Participant 3, "it addresses underreporting; just because somebody had something happened." According to Participant 18, "Benefits are as discussed for FAERS only the extremely adverse events get reported."

Threats to public health. According to Participant 2, "I say society it means all the players who are responsible for managing healthcare in the system." The adverse effects of drugs pose threats to public health. According to Participant 1, "Then we also have issue with health plan if there is like common center dealing with all these information."

Health safety. According to Participant 1, "it will help them to reduce safety issues that what we have and they could help with prescribing activities and it all helps the healthcare system in itself." Participant 2 likewise mentioned, "The potential benefits of the patients ultimately the FDA was created to benefit the patients and consumers and the larger population will be benefited by this and more genotyping & genomics data." Health safety of patients can be achieved if drugs are safe.

Patient-centeredness. According to Participant 5, "Sentinel because if the data info collected on patients through insurance companies." Quoting Participant 20, "I think it's mostly patients safety, they are having a lot of information sharing it they are able to share it, they are compiling they are getting a great deal more info on all these products hopefully to be used for a patient safety." FAERS and Sentinel Initiative are focused on the welfare of patients.

The FAERS and Sentinel Initiative were forms of surveillance that attempted to enance the vigilance of the public towards responsible data collection on the adverse effects of drugs. Participant 17 was quick to note the importance of data collection because the availability of data was relevant to have durable information which could help in the advancement of health. An active system of data collection allowed immediate

results. The voluntariness of reporting was also a positive factor to ensure that adverse drug reactions were protected. The accuracy of the information and the speed of obtaining information were some of the benefits that could be derived from Sentinel Initiative. As the more proactive surveillance mechanism, Participant 14 said that:

> Benefits will be the speed of obtaining information and the accuracy of the information being reported. What I understand from the system, it seems that there is some confusion, chances are that you will have to go to the source that has provided the information.Going to the source that has provided the information, it will be one or two people; instead of going to the whole range of people that are involved even. Even though it's a new way of collecting the AE [adverse events], this might be a speedy process. Negative factor- it might be I am not 100 % sure it might have effect pharmaceutical companies.

Preventive Measure. The data available using the surveillance methodologies in the field of pharmacy should be more inclusive and open to the public. It should be emphasized that the main reason behind the data collection of ADRs was to ensure that future negative effects would be prevented.

Preventive action. The reporting model was a form of preventive action to ensure that future similar incidents would be prevented. Quoting Participant 13, "I think there are may be 18 organizations collecting this data help data warehousing and ensure companies like that have access to vast of data and vast of health data." The purpose of Sentinel and FAERS should go beyond mere research. The awareness of the public should be increased by making the data available to third parties, thus enhancing the vigilance of drug users. As pointed out by Participant 6:

> Since the data is mentioned by those organizations or plans, and at this point only FDA is accessing this data, only FDA is approved for accessing the data so it is really not true data for drug safety purposes, and FDA using it for the lack of any other method out there for using this system, so that I would call it a challenge,

> when we have that anybody can access that data space, where anybody can access and get information about a potential drug reaction and so on. That day is far away. Even after all they say that Sentinel system is augmented FAERS system, we still have that challenge out there.

Alerting the public. According to Participant 4, "So like I told you earlier people were not aware about these portals and reporting of various drug problems since it's a common interaction between the doctor and the patient." Participant 17 noted that, "The potential challenges which I am looking upon in this under reporting of adverse from these methods is to instill a sense of security amongst the patients and we have to educate them that their personal data is only used for medicinal and research purposes." The public has the right to know on the possible adverse drug effects based on the experience of others.

Evidence-based. The reporting of adverse drug effects by the patients will allow evidence-based conclusions. Quoting Participant 19, "Doctor must have prescribed something and there must be some evidence and records they don't have to wait for many years."

Vigilance. Participant 16 mentioned that, "I mean all the stakeholders that are involved should be responsible whether be the manufacturers or the distributors or the FDA or the healthcare professionals or even the patient." Vigilance in the pharmaceutical industry must be improved. Participant 17 was quick to note the importance of data collection because the availability of data was relevant to have durable information which could help in the advancement of health.

Drug Manufacturer. The FAERS surveillance system was beneficial in pharmacovigilance because it monitored the adverse reactions to drugs and medication.

Monitoring the adverse reactions added to the information available to the public domain. The public and the patients benefit from the surveillance systems. The patients were now more informed about the consequences of the medicines that they take. The pharmaceutical companies and health agencies also benefitted from the reports. The pharmaceutical companies would become more vigilant in ensuring that the products are safe. Because of the mechanism to report and self-report the adverse reactions, the companies that manufacture drugs would now be more careful in the advancement of the safety of the medicine. The use of health data was one of the advantages in the use FAERS. Health data that was voluntarily given to the FDA could create an awareness to the general public. The availability of the information that could readily be accessed by the public was one of the benefits of the FAERS.

Drug safety. According to Participant 17, "It will help derive the FDA and to evaluate about a drug and take some safety measures about a drug." Drug safety should be prioritized in ensuring that there were proper reportorial mechanisms.

Opportunity to improve healthcare. Quoting Participant 5, "So the challenge again would be the lack of partnership, they have to increase their partnership to all physicians, pharmacies in order to expand their data base." Healthcare professionals would improve their performance if the drugs were properly regulated.

Disease occurrence. Disease occurrence could be lessened if there was proper regulation of drugs available in the market. Participant 19 noted that, "There are some other diseases and other things that I have and if I am going to take this medication it going to have an impact on me."

Other Stakeholders. The scope of the Sentinel Initiative could be enhanced. More stakeholders should be considered. The presence of more stakeholders would make the benefits and advantages of the policies more comprehensive and encompassing. The awareness of the people about these surveillance systems should be enhanced. The self-reporting requirements should be more active. More people should be able to access the information. The information collected should not be limited for research purposes but should actually include having relevance to the general public.

According to Participant 5, there was a need to obtain more stakeholders to improve the performance in the reportorial requirements. It could be said that the inclusion of more stakeholders would make the drug companies more proactive because more interested parties would be affected by their actions:

> They will need to obtain more stakeholders so I don't think they have a method to handle the under reporting of drug reactions so it doesn't seem that they have a separate method they can use to overcome under reporting of worst events so if the data is not there they can obtain any additional information.

Accessibility. Participant 5 noted that, "Consumer may not allow releasing their health care info and they need to increase their stakeholders if they want to expand and implement all over the country." A more inclusive progress in the field of pharmacovigilance was possible if there were more stakeholders.

Inclusive. It was noted by Participant 5 that, "To obtain extensive stakeholders and partners to participate in this initiative there will have to some kind of method to educate consumer for this work so that they may be able to share their health care info to

the database." A more inclusive system should be created so that the development would go beyond research purposes.

Discovery of new risks. New risks on the adverse drug effects would be prevented. As mentioned by Participant 4, "That it can eliminate under reporting to extent but it will be still be there because the access to data is small and I think they are also working on it once data bases are linked and they have access to those databases then they will have better analysis to problems of adverse drug reactions."

To summarize, it could be concluded that the adverse effects of drugs would be recognized and the safety of the patients and the public would be prioritized. The presence of FAERS and Sentinel Initiative improved the vigilance of the public towards the adverse effects of drugs. A more inclusive database would include other stakeholders and make the records more accessible. The availability of a surveillance system such as FAERS and Sentinel Initiative would improve drug safety.

Theme 2. FAERS and Sentinel Initiative provide a systematic data collection for a database that would use health data to improve public health.

The FAERS was beneficial because it was a form of data collection that was based on the voluntary reporting of individuals, patients or physicians that suffered from ADRs. It was beneficial because the patients voluntarily report the data and not based on compulsory requirements mandated by regulations. Further, the FAERS surveillance system allowed the pulling out of the market, the drugs that were proven to be detrimental to the health of the public.

Data collection. Participant 17 noted that, "The availability of vast volume of data which includes not only the drug reaction details but also the information such as medical history of the patient, personal details such as age etc. also all this information will help us derive relevant and durable information from the data." FAERS and Sentinel collected data from patients regarding the adverse effects of drugs.

Use of health data. Health data was used for the record of FDA. According to Participant 14, "There are various organizations and to be exact I believe 18 organizations that are involved in retrieving health data."

Active system. The Sentinel Initiative was an active system of reporting. As observed by Participant 4, "So benefits like I told you that it's an active system they have immediate results." According to Participant 17, "Benefits will be the speed of obtaining information, the accuracy of the information being reported and there seem for what I understand from the system there seem that if there is some confusion."

Voluntary reporting. The voluntariness of reporting was evident in the regulation. According to Participant 1, "FAERS is basically everything is voluntarily done most of the time it is more specific to particular patients." According to Participant 6, "All those drug adverse reports either directly send to FDA or they are sent by the manufactures to FDA are entered in FAERS. The biggest issue here in this whole exercise is that reporting a drug adverse reaction is not required by law or anyone else but it's an voluntary basis exercise."

Systematic database. Quoting Participant 7, "FAERS is the FDA adverse events reporting system. It's a database that contains the information on adverse events (AEs)

and medication errors." Reporting the adverse drug reactions allowed having a present systematic database. According to Participant 4, the Sentinel initiative, "That it can eliminate under reporting to extent but it will be still be there because the access to data is small and I think they are also working on it once data bases are linked and they have access to those databases then they will have better analysis to problems of adverse drug reactions."

Privacy. Privacy of the individuals who reported adverse effects might be at stake. According to Participant 6, "I really see here is the privacy issue- the HIPAA compliance. I don't know if the patients would like to share their information to a third party." Participant 5 mentioned that, "Adherence to privacy laws, consumer may not allow to release their health care info and they need to increase their stakeholders if they want to expand and implement all over the country."

Relative assessment. There could be differences in how a person assessed or evaluated the effects of drugs. According to Participant 8:

> With the FAERS system addressing adverse differential FAERS is dependent on whether the patient really calls FDA or health care company and that one is limited. Whereas with Sentinel the patient may be either talking to healthcare profession that I had reaction with drug and it might get reported much more better than the FAERS system where the patient might even not know where to report.

The Sentinel could be a great help in ensuring that all adverse reactions to a drug were reported. It was to be noted that underreporting must be discouraged because failure to notify the FDA regarding certain instances may pose danger to the lives of future users of the medication. Participant 17 further noted that:

> Sentinel Initiative address uneven quality of adverse drug reactions reports compared to FAERS just like in FAERS is a voluntary system where in

> the patients report themselves about a serious suspected drug reaction and information can be limited so it can be difficult for the FDA to decide whether an adverse reaction is serious or not and it can be difficult for the FDA to take some safety measures against the drug.

The FAERS surveillance methodology was perceived to be a passive methodology. This was contrasted with the capability of the FAERS wherein there was a less number of population reached. According to Participant 6, the Sentinel surveillance methodology was an improved way of collecting data because it was more active as it was highly imposed and regulated:

> Per the latest estimate, there are about 18 organizations participating and FDA can access the medical data of almost 178 million patients through this initiative. Since the data is maintained by the organizations/plans using a common data model, it's an example of distributed database. This system is available to FDA only for monitoring the post-marketing product safety information. A query is entered into the system and FDA can have the information from this vast data of 178 million patients on need basis. Because of the nature of information retrieved from this vast data, the Sentinel initiative is so called "active" system. Why I'm calling it "Active" because the data is coming from HMOs plans, hospitals, and other medical centers where the data is entered by the health care professional while they are consulting or treating a patient. So I would say that the Sentinel initiative is augmented the FAERS system.

The same participant was of the observation that the Sentinel was better in terms of data collection and was a far cry from the passive FAERS system where compliance seemed to be optional, "All those drug adverse reports either directly send to FDA or they are sent by the manufactures to FDA are entered in FAERS. The biggest issue here in this whole exercise is that reporting a drug adverse reaction is not required by law or anyone else but it's an voluntary basis exercise."

To summarize the second theme, it could be inferred that FAERS and Sentinel Initiative provided a systematic database that would use health data to improve public

health. Having a systematic mode of data collection would allow the careful sorting of what was relevant and what was not. Data collection of adverse drug effects would also help in research and prevention of ADRs in the future.

Theme 3. The reporting model provides a regulatory mechanism after the drug approval activities in order to evaluate the medicinal products.

The FAERS and Sentinel Initiative provided a good regulatory mechanism because the FDA would have access to vital information to monitor and evaluate the adverse effects of drug products. One of the challenges in FAERS was that it was a mere passive way of reporting data to the FDA. Underreporting was prevalent in the FAERS system because of the lack of mechanisms to ensure that each ADR is brought to the attention of the FDA. According to Participant 7, there are many challenges to the current FAERS:

> The current FAERS system doesn't have a good picture, there is not necessarily a good population size and not an easy way to interpret the data with the advanced analysis. So for the electronic healthcare data source, we will be tracking millions of patients and will also contain more comprehensive and complete information for the patients that are in the system. We will maximize the efficiency of the risk identification system, and also the incidents of reporting will be detectable and accurate.

The access to data in the FAERS system was also a challenge. Scientists of the FDA were not able to access the reports reported to FAERS on a real time basis. This posed great threats to the safety of the public when the data could not be divulged to the public in a prompt manner. As observed by Participant 10:

> As I said earlier, scientists will have capabilities to find the answers to some of their questions in weeks, which with the FAERS systems used to take months or sometimes even longer, so that's one of the benefits I see. With that it will hub that to go towards right research, not like they did

> research for 5 years and then figure out okay, this is not going to help. So probably getting the right kind of remediation, I don't have the right word but finding right resolutions for particular health problems I think this system would help.

Sentinel Initiative and FAERS had challenges and negative impacts because of lack of an effective and efficient regulation to ensure that the purpose was served. There was lack of responsibility in the implementation and evaluation.The rules should be more specific in pointing out the certain responsibilities and accountability of the different government agencies such as the FDA. The data collected might not be valuable for the human public because it was not accessible. There could be an issue of privacy in the reporting requirements. As in other policies, the issue of privacy in the reporting of adverse impacts could be a major concern of patients and other affected individuals.

One disadvantage of the Sentinel Program was the lack of responsibility in the implementation and evaluation. There was a system of notification but the liability of the drug companies was not clear. There was no system of going to the next step once the effects of notifcation had been sent to the FDA. As pointed by Participant 19:

> An international body that's like they call it an international conference on humanizations and then they came up with the guidelines and that guidelines helped us to build that system, the FDA adversary reporting system. The one is based on the guidelines and in that FAERS the manufacturers is responsible to notify as the drug is out in the market they just have to notify the market if there is any event related to that drug.

A challenge posed in the evaluation of the methhods in FDA Sentinel was the fact that the data collected might not be collected for research purposes. There was a need to ensure that the validity of the coding would be maintained. According to Participant 11, the FDA should be responsible in the implementation of the methods in this policy

because “they need all that information to make the assessment and to approve or disapprove you know drugs on the market so they should want to have the best surveillance system out there.” The following explained the different codes associated to this formed theme:

Risk evaluation. Participant 13 mentioned that, “I think the challenges are that you know with a lot of data you also comes with it is noise and you know the quality of data and probably you can have where signals will get lost and then you have different interpretations of signals of what is actually a risk and what is I think it gets a little bit murky with that large amount of data.” The risks on drugs would properly be assessed if there was a proper reporting model.

Reporting model. Participant 5 noted that, “It doesn’t seem that they have a separate method they can use to overcome under reporting of worst events so if the data is not there they can obtain any additional information.” The reporting model of how adverse drug effects were recorded should be systematic. As mentioned by Participant 17, “The sentinel would help make the data more reliable removing the underreporting of several adverse drug reactions by it will flood the data with records which people earlier used to think may be irrelevant or not necessary and sufficient to be reported.”

Post-drug approval activities. According to Participant 4, “So basically they use all these query methods so that they can query these large database to determine to get the desired results of what are on what features are they looking for and what kind of problems they want to solve or especially what drug they want to improve.” Post-drug approval activities must be evaluated to ensure the safety of the public.

Evaluation of products. The proper evaluation of products should be the priority in order to ensure health safety. According to Participant 18, "Evaluation is done principally by FDA and they will be the one who will analyze the data and gather critical information out of this." Participant 9 mentioned that there could be regional restrictions for the study itself because the usage of the drug could be much wider in region than compared to other regions.

Responsibility. There should be a government agency that regulates drugs in order to monitor responsibility on the safety of drugs. Participant 20 mentioned, "So here again I think the agency has the ultimate responsibility when it comes to reporting though in general it is on … it's on the health care professionals and consumers."

The relativity of determining whether a certain effect was adverse or not was a consideration that posed challenge to the effectiveness of the Sentinel surveillance policy. Participant 9 mentioned that there could be regional restrictions for the study itself because the usage of the drug could be much wider in region than compared to other regions. The funds were also challenges to the methods of reporting. According to Participant 2:

> What you call adverse reaction may not be adverse reaction historically the away FDA has taken the stance like sometimes because they are free to report it o media they are free to report it to pharma company they are free to create out a norm that you to have to pull out the drug from the market these are the sensitive thing so its is up to the pharma companies to take a stance and really help FDA to understand or keep a list of things I am just simplifying things a little bit but these are the risks.

As in any program or policy, the issue of privacy was a big consideration in determining the impact and challenges to a specific program. According to Participant 7, the privacy

of the patients could also be compromised with the new reportorial requirements. Privacy concerns were also raised by Participant 5:

> So right now there is limited data source and have 17 partners right now and to this be able to work they will have to expand and their data sources to a great deal, funding will be another challenge, adherence to privacy loss, consumer may not allow to release their health care info and they need to increase their stakeholders if they want to expand and implement all over the country and internationally as worse event and signal collection is worldwide just the USA , right now the sentinel would be limited USA.

There was a need to include more organizations to cooperate with the Sentinel Initiative. Currently, there were only 18 organizations that were part of this policy. According to Participant 12, "So one of the major disadvantages or challenges that have been referred to that I see is that there are only 18 organizations that are currently involved so I feel like that would limit the sentinel initiative so there need to be more organization that need to be involved I feel to deal with this challenge." There was a need to focus on including more organizations so that the data collected by FDA would be more comprehensive and the information made available to the public would be more complete and relevant.

To summarize the third theme, it could be concluded that the presence of a reporting model provided a regulatory mechanism after the drug approval activities in order to evaluate the medicinal products. A regulatory mechanism would decrease the voluntariness of reporting and allow a more systematic way of monitoring the adverse drug effects. Further, the regulatory mechanism would hold a specific government agency accountable for the evaluation of the effects of drugs.

Responses to the Research Questions

RQ1. The results of the study answered the three research questions originally posed. The first research question asked the prospective benefits of the FDA's Sentinel Initiative as compared with the FAERS surveillance methodology. Sentinel Initiative and FAERS were beneficial in pharmacovigilance because they monitored the adverse reactions to drugs and medication. Monitoring the adverse reactions added to the information available to the public domain. The public and the patients benefitted from the surveillance systems. The patients were now more informed about the consequences of the medicines that they took. The pharmaceutical companies and health agencies also benefitted from the reports. The pharmaceutical companies would become more vigilant in ensuring that the products were safe. Because of the mechanism to report and self-report the adverse reactions, the companies that manufacture drugs would now be more careful in the advancement of the safety of the medicine.

The Sentinel could be a great help in ensuring that all adverse reactions to a drug were reported. As mentioned by Participant 17, “The sentinel would help make the data more reliable removing the underreporting of several adverse drug reactions by it will flood the data with records which people earlier used to think may be irrelevant or not necessary and sufficient to be reported.” As a more active way of getting information to monitor adverse drug effects, Sentinel Initiative promised a more reliable source of data available for the public and for pharmaceutical companies. Further, the Sentinel Initiative was a more inclusive way of providing information to the public.

The FAERS surveillance methodology was perceived to be a passive methodology. As observed by Participant 9, the capturing of data in Sentinel was more proactive and real time data was collected. The same participant was of the observation that the Sentinel was better in terms of data collection and was a far cry from the passive FAERS system where compliance seemed to be optional, “All those drug adverse reports either directly send to FDA or they are sent by the manufactures to FDA are entered in FAERS.” In FAERS, it can be said that there was already accountability on the part of FDA.

RQ2. The second research question asked the challenges and negative impacts of the FDA's Sentinel Initiative as compared with the FAERS surveillance methodology. Sentinel Initiative and FAERS had challenges and negative impacts because of lack of an effective and efficient regulation to ensure that the purpose was served. There was lack of responsibility in the implementation and evaluation. The rules should be more specific in pointing out the certain responsibilities and accountability of the different government agencies such as the FDA. The data collected might not be valuable for the human public because it was not accessible. There could be an issue of privacy in the reporting requirements. As in other policies, the issue of privacy in the reporting of adverse impacts could be a major concern of patients and other affected individuals.

One disadvantage of the Sentinel Program was the lack of responsibility in the implementation and evaluation. The relativity of determining whether a certain effect was adverse or not, was a consideration that posed challenge to the effectiveness of the Sentinel surveillance policy. Participant 9 mentioned that there could be regional

restrictions for the study itself because the usage of the drug could be much wider in region than compared to other regions.

RQ3. The third research question asked the lessons learned that could enhance the scope of the Sentinel Initiative. The scope of the Sentinel Initiative could be enhanced. More stakeholders should be considered. The presence of more stakeholders would make the benefits and advantages of the policies more comprehensive and encompassing. The awareness of the people about these surveillance systems should be enhanced. The self-reporting requirements should be more active. More people should be able to access the information. The information collected should not be limited for research purposes but should actually include having relevance to the general public. There were some instances where the performance in pharmacovigilance could be improved from the current set up of FDA's Sentinel. There was a possibility of tracking back the results and effects of a certain drug and medication so that it could be comprehensively studied and researched.

Inclusion of more stakeholders. The scope of the Sentinel Initiative could be enhanced. More stakeholders should be considered. The presence of more stakeholders would make the benefits and advantages of the policies more comprehensive and encompassing. The awareness of the people about these surveillance systems should be enhanced. The self-reporting requirements should be more active. More people should be able to access the information. The information collected should not be limited for research purposes but should actually include having relevance to the general public.

More active self-reporting requirements. The reporting model of how adverse drug effects were recorded should be systematic. Post-drug approval activities must be evaluated to ensure the safety of the public. The requirements to report must be more stringent. The information must be used by the FDA to improve data collection and establish a safer method of drug manufacture. As mentioned by Participant 17, "The sentinel would help make the data more reliable removing the underreporting of several adverse drug reactions by it will flood the data with records which people earlier used to think may be irrelevant or not necessary and sufficient to be reported."

Summary

There were various reasons why FAERS and Sentinel Initiative were effective surveillance methodologies to enhance pharmacovigilance. The Sentinel could be a great help in ensuring that all adverse reactions to a drug were reported. The availability of the information that could readily be accessed by the public was one of the benefits of the FAERS. On the other hand, the accuracy of the information and the speed of obtaining information were some of the benefits that could be derived from Sentinel Initiative.

While there are benefits and advantages, there were also challenges related to the implementation of either FAERS or Sentinel Initiative. One disadvantage of the Sentinel Program was the lack of responsibility in the implementation and evaluation. There was a system of notification but the liability of the drug companies was not clear. A challenge posed in the evaluation of the methods in FDA Sentinel was the fact that the data collected may not be collected for research purposes. There was a need to ensure that the validity of the coding would be maintained. As in any program or policy, the issue of

privacy was a big consideration in determining the impact and challenges to a specific program. There was a need to include more organizations to cooperate with the Sentinel Initiative.

There was a need to enhance the scope of Sentinel Initiative to make it a more effective way of surveillance for pharmacovigilance. It could be said that the inclusion of more stakeholders would make the drug companies more proactive because more interested parties would be affected by their actions. The awareness of the people and the patients should be improved in order to increase the effectiveness of the Sentinel surveillance system. With the awareness that data could be accessed to inquire about certain information on the effects of medication, the patients would become proactive in interacting with the doctors. The data available using the surveillance methodologies in the field of pharmacy should be more inclusive and open to the public. This would ensure that the welfare of all the stakeholders in the pharmaceutical industry would be protected.

Chapter 5: Discussion

The current FDA consumer safety surveillance system used FAERS for reporting adverse events involving pharmaceutical drugs (FDA, 2012a; Powers & Cook, 2012). The FAERS used a database designed to assist the FDA and its partners in monitoring postmarketing safety of approved drugs and other biologic products (Powers & Cook, 2012). However, the FAERS had limitations such as not reporting real-time data collection (FDA, 2012a). Therefore, the FDA launched the Sentinel Initiative in 2008. The FAERS and Sentinel Initiative were adverse drug reaction (ADR) reporting systems. This study addressed the lack of research regarding the impact of Sentinel Initiative compared to the FAERS. It was necessary to assess the benefits and challenges associated with the FDA's Sentinel Initiative compared to the current FAERS surveillance methodology.

According to the FDA (2012a), the FAERS had (a) a system for reporting the adverse effects of drugs, and (b) a database for these reported cases of ADRs. The Sentinel Initiative was a national electronic system for monitoring the safety of FDA-approved drugs and other medical products (FDA, 2012d). The Sentinel system was developed and implemented as an aid to the existing FAERS. The FAERS did not make use of real-time data, which referred to the precise time or location that a drug was used or consumed by the market members (Gottlieb, 2005). Presently, the reporting system used by the FAERS was voluntary and quarterly (Powers & Cook, 2012). Instead of depending on point-of-care data collection, the Sentinel Initiative could access multiple

existing data systems such as electronic health record systems and medical claims databases (Platt et al., 2009).

The purpose of this qualitative comparative case study was to examine the FAERS surveillance system and the FDA's Sentinel Initiative to determine the benefits and consequences of the Sentinel Initiative in terms of drug consumer safety. This qualitative study included the perceptions of individuals who had worked closely with FAERS program and were aware of the Sentinel Initiative. I interviewed key informants who worked with FAERS andwere familiar with the Sentinel Initiative to better understand their perceptions of the differences between these two programs.

The results of the study answered the three research questions originally posed. The first research question addressed the prospective benefits of the FDA's Sentinel Initiative as compared with the FAERS surveillance methodology. Both programs were beneficial in pharmacovigilance because they monitor the adverse reactions to drugs and medication. However, I found that the Sentinel system could be a great help in ensuring that all adverse reactions to a drug were reported. Participants also described the FAERS surveillance system as a passive methodology. One participant pointed out that the Sentinel was better in terms of data collection and was superior to the passive FAERS system in which compliance seemed to be optional. Participants reported that the FDA's Sentinel Initiative was better than the FAERS surveillance methodology. wasThe results of this study provided information regarding the effectiveness of the FAERS and the Sentinel Initiative. No current study compares experts' perceptions of the FDA's Sentinel Initiative and the FAERS surveillance methodology.

The second research question addressed the challenges and negative impacts of the FDA's Sentinel Initiative as compared with the FAERS surveillance methodology. Both programs had challenges and negative impacts because of lack of effective and efficient regulation to ensure that the purpose of the two systems is served. There is also an issue of privacy in the reporting requirements. One disadvantage of the FAERS surveillance methodology is not being able to use real-time data. One disadvantage of the Sentinel program was the lack of responsibility in implementation and evaluation of data collected through the Sentinel. The relativity of determining whether a certain effect was adverse or not, it was a challenge to the effectiveness of the Sentinel surveillance policy. Both programs had advantages and disadvantages. The FAERS surveillance methodology was seen as a weaker methodology because it could not use real-time data and had a small database compared to the Sentinel surveillance. However, there was lack of accountability in the implementation and evaluation of the Sentinel Program.

It was important to determine the advantages of the Sentinel Initiative because insights from this study could support the FDA's efforts to improve reporting systems to detect ADR. Robb (2012) described the advantages of the Sentinel program such as using voluntary participants to have an active safety surveillance system. Moreover, within 2 years of its existence, the Mini-Sentinel program had 31 academic and private organizations associated with it (Platt et al., 2012). Additionally, Forrow et al. (2012) asserted that the Mini-Sentinel program is remarkable because it had its own organizational structure as well as principles that regulate its operations.

The third research question addressed the lessons learned that could enhance the scope of the Sentinel Initiative. The study indicated that the scope of the Sentinel Initiative could be enhanced; however, more stakeholders should be considered to make the advantages of the policies more comprehensive and encompassing. Awareness of these programs should also be improved so that more individuals would be able to access the information. No study had been conducted to examine the changes that should be made to the Sentinel Initiative for it to improve.

In this chapter, the results of the study were interpreted and the implications of the findings were explained. The study limitations were also described and future research recommendation was also provided. The chapter is concluded with the summary.

Interpretation of the Findings

Theme 1. The presence of FAERS and Sentinel Initiative improves the vigilance of the public towards the adverse effects of drugs and promotes health and public safety. Three themes emerged from the data analysis. First, the presence of FAERS and Sentinel Initiative improves the vigilance of the public regarding the adverse effects of drugs and promotes health and public safety. Second, the FAERS and Sentinel Initiative provide systematic data collection for a database that uses health data to improve public health. Third, the reporting model provides a regulatory mechanism after the drug approval activities in order to evaluate the medicinal products.

Theme 1

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The first finding is that the presence of FAERS and Sentinel Initiative improves the vigilance of the public regarding the adverse effects of drugs and promotes health and public safety. This theme was derived from the following categories: data collection, patient's health, regulatory mechanism, preventive measure, other stakeholders, and drug manufacturer. In relation to the problem statement, the results indicated that both programs had advantages and disadvantages. The participants confirmed that both programs had the ability to make individuals vigilant about adverse effects of drugs. However, the participants emphasized that the Sentinel Initiative was better because it used an active system of reporting that brought immediate results. Moreover, the Sentinel Initiative was better when it came to relative assessment of patients because the patient might talk to an experienced health care professional, which is better than the FAERS system in which the patient might not know where to report.

This finding confirmed existing literature about ADRs. Both the FAERS and Sentinel Initiative improved pharmacovigilance of the public regarding the adverse effects of drugs and promoted health and public safety. Behrman et al. (2011) stated that the FDA Sentinel Initiative served as an additional tool for the FDA to evaluate the safety of medical products and acted as a national resource for the FDA to take advantage of investigating medical product performance. Additionally, the Sentinel Initiative would become a national resource of a learning health care system. The Sentinel Initiative enhances existing health care information to allow the FDA to perform active post-market safety surveillance in support of the current surveillance systems had(Robb et al., 2012). In a recent study, Sarntivijal and Abernethy (2014) found that Internet search logs

could also be complementary to the evaluation of FAERS reports. Henceforth, it showed there were many methods of reporting of adverse events were evaluated by stakeholders than just simply relying on the FAERS.

Using FAERS and the Sentinel Initiative, the FDA can scrutinize regulated medical products nearly as fast as real time to better comprehend product safety (Robb et al., 2012). The Sentinel Initiative aided the FDA in discovering and analyzing post-market safety signals through signal generation, signal refinement, and signal evaluation, which referred to the concern over an excess of irregular and negative events when compared to what was traditionally associated with a product's use (Robb et al., 2012). Moreover, the Sentinel Initiative was helpful to the FDA in making regulatory decisions (Robb et al., 2012).

Several researchers supported the use of the Sentinel Initiative through the Mini-Sentinel program. The Mini-Sentinel program was a pilot under the FDA Sentinel initiative, as an effort to implement a national system that would assess the safety of medical products. Mini-Sentinel was successful in serving as a general-purpose vaccine safety monitoring system (Robb et al., 2012). Platt et al. (2012) found that the Mini-Sentinel program employed various activities such as robust surveillance of a wide range of drugs and vaccines, as well as improving the common data model to secure additional types of data. According to Forrow et al. (2012), the Mini-Sentinel program was remarkable because it had its own organizational structure as well as principles that regulated its operations. These policies and structures allowed it to influence the structure and purpose of the Sentinel system (Forrow et al., 2012).

In the context of the theoretical framework, this finding is consistent with theory of preemption, which asserts that it was important to use information to make sound judgments regarding issues or activities of national importance, such as prescription drug-related regulations. The existence of FAERS and Sentinel Initiative provide current, accurate, and actionable information to the FDA to ensure consumer safety, especially in detecting uncommon cases of product exposures (Platt et al., 2009).

Due to the FAERS and Sentinel Initiative, adverse effects of drugs would be recognized and the safety of the patients and the public would be prioritized. As a result of the FAERS and Sentinel Initiative, the public will become more vigilant regarding the adverse effects of drugs. Thus, the FAERS and Sentinel Initiative would improve drug safety and public health as both systems complements each other for adverse event reporting. The patients' safety is enhanced due to existence of both the methods in place.

Theme 2

The second finding was that FAERS and Sentinel Initiative provided a systematic data collection for a database that would use health data to improve public health. Systematic data collection was included in pharmacovigilance. Pharmacovigilance activities encompassed the collecting, exchanging, accumulating, analyzing, interpretation, and sharing of data regarding the experiences of patients who had used a specific drug or certain therapeutic agent (van Grootheest & Richesson, 2012). In relation to the problem statement, study findings indicated that both programs provide systematic data collection for a database. One of the problems in this study was to determine whether the Sentinel Initiative was more effective as compared to FAERS. The accuracy

of the information and the speed of obtaining information were some of the benefits that could be derived from the Sentinel Initiative. The Sentinel surveillance methodology was an improved way of collecting data because it was more active as it was highly imposed and regulated. Moreover, the Sentinel Initiative could be a great help in ensuring that all adverse reactions to a drug were reported. Moore, Furberg, Mattison, and Cohen (2016) concluded that Sentinel surveillance methodology was a better way to collect data to assess adverse drug events reported to the FDA.

This finding confirmed existing literature about the importance of having systematic data collection. Researchers emphasized the importance of systematic detection and assessment practices that could handle adverse drug effects (van Grootheest & Richesson, 2012). Hoffman, Overstreet, and Doraiswamy (2013) stated that more than 770,000 injuries or deaths annually could be attributed to adverse events linked to drugs already approved by the FDA. Hoffman et al. stated that approximately 28% of these adverse events could be prevented if there was an effective computerized monitoring system in place. Through systematic data collection, thousands of individuals could be saved from the side effects of the drugs they used before a clinician could be subjected to public investigation and action (van Grootheest & Richesson, 2012). FAERS had the ability to acquire 700,000 reported adverse events annually across different therapeutic categories, making it a powerful database (Hoffman et al., 2013).

Systematic data collection was also important for adverse drug reactions (van Grootheest & Richesson, 2012). If an adverse drug reaction was suspected, then trials and tests would have to be carried out to confirm or refute the suspicion. Before tests were

carried out, careful and systematic collection of data was necessary (van Grootheest & Richesson, 2012).

The case of banning thalidomide from the market was the result of systematic data collection (van Grootheest & Richesson, 2012). The case propelled the FDA to start a systematic collection of ADR reports to identify drugs that would harm individuals. Other countries followed suit and developed new rules and regulations that organizations needed to adhere to before releasing a new drug in the market.

In the context of the theoretical framework, this finding was consistent with the theory of preemption, which is applied in the analysis of useddata to make market-based decisions regarding drug safety (Gostin, 2011). The theory of preemption also involves using data from ADRs and cases to address the damages experienced by affected consumers (Valoir & Ghosh, 2011). Thus, systematic data collection was needed to protect the health of the public.

The FAERS and Sentinel Initiative provided a systematic database that professionals and experts can use to improve public health. A systematic mode of data collection would filter what was relevant and what was not. Data collection of adverse drug effects would help in research and prevention of ADRs in the future. Moreover, reduction of ADRs could save thousands of lives.

Theme 3

The third finding was that the reporting model provided a regulatory mechanism after the drug approval activities in order to evaluate the medicinal products. One of the challenges observed in FAERS was that it was a more passive way of reporting data to

the FDA. In fact, reporting could be optional. Moreover, the reports sent to FAERS could not be accessed on a real-time basis. This was a threat to the safety of the public when important health data could not be divulged to the public in a prompt manner. Both the FAERS and the Sentinel Initiative could be improved through responsible implementation and evaluation.

This finding extended existing literature about the importance of having a reporting model. The main motivation behind reporting models was to ensure public safety and the main strategy was still population monitoring (van Grootheest & Richesson, 2012). Reporting model was included in pharmacovigilance. Reporting models were important because in pharmacovigilance, there was an assumption that all therapeutic agents had a specific level of risks and these risks were not equally distributed across the population. Thus, some groups were more likely to suffer from ADRs compared to others (van Grootheest & Richesson, 2012). It was important to monitor and to warn individuals of the possible side effects or adverse effects of the drug. Raine (2012) emphasized that harmful effects from drugs should be monitored, as they could be deadly and costly to the healthcare sector. Raine asserted that costs of adverse effects of drugs could be greater in developing countries than in developed countries. Adverse incidents might have a negative impact to the credibility and success of important public health programs (Raine, 2012). In order to improve pharmacovigilance strategies, WHO also asserted that there should be efficient and effective planning and implementing of ADR surveillance systems (Raine, 2012).

In the context of the theoretical framework, this finding was consistent with theory of preemption. The theory asserts the significance of data in make sound judgment regarding issues or activities of national importance such as public health. A reporting model was important because it provided a regulatory mechanism after the drug approval activities in order to evaluate the medicinal products. A reporting model should be developed because it would help in the systematic collection of data regarding adverse drug effects. Moreover, a specific government agency might be held accountable for the evaluation of the effects of drugs.

Limitations of the Study

There were many limitations in this study such as researcher bias, sample size, instrument, and data collection bias. Each limitation had an impact on this study and every effort was done to control the effects of the limitations. One such limitation of this study was researcher's bias. The researcher had extensive knowledge of ADRs and pharmacovigilance systems. In order to mitigate this bias, the researcher took data collected during participant interviews as is and conducted member checks to ensure that the interpretations made were consistent with the actual interpretations intended by the participants. This limitation might have an effect on the interview guide/questions used for data collection. Recognizing this, the interview guide/questions were written without bias and to allow the participants to use their experiences and knowledge to answer the questions.

Another limitation was the sample size. There was the possibility of not obtaining enough participants. Key informants included drug company safety professionals who

had self-reported knowledge or expertise in assessing consumer impact. However, the study got enough participation from the sample group. The study was also limited to aim for 20 participants with the consideration of data saturation. The limited sample size indicated that the findings of the study might not be generalizable.

Another factor that may result to inadequate results was poorly developed interview questions. The interview guide was developed properly to be open-ended, specific enough to avoid confusion, and be easy to understand. To avoid this pitfall, great care was applied in development of the interview guide.

Another limitation was the research methodology chosen. However, qualitative design was appropriate because existing research in the area is limited. Qualitative methodology allowed for rich description of the phenomenon.

Recommendations for Future Research

First, future researchers could extend the study to include not only the key informants but also the consumers as well. Perception of the consumers regarding the surveillance systems could also aid in development of policies and programs to improve them. Moreover, perspectives of the consumer were significant since the consumers would be the one who would experience the adverse drug effects.

Second, future researchers could also think of other factors that could influence the effectiveness of the two programs. Most consumers were hesitant to report adverse drug effects. This might be one of the reasons a reporting model might not be successful.

Third, future researchers could use a different measurement or data collection tool. Data from the two programs could be used to determine whether health data in the program actually improved public health. Moreover, documents could also be examined.

Lastly, future researchers could use quantitative methodology or mixed methods. Quantitative methodology allows for collecting data from a large sample size. The size of sample size in quantitative studies could mean that it was representative of the whole population.

Implications of the Findings

The findings of this study had potential impact for positive change at the societal level, organizational level, and individual level. At the individual level, individuals were more vigilant about adverse effects of drugs and aware that they should report adverse effects. At the organizational level, manufacturers of drugs would be informed of the adverse effects of their drugs. Perhaps, the manufacturers could develop new drugs with less possibility of adverse effects. At the societal level, policies about drug safety would be modified to benefit the public.

The findings of the study were consistent with the theory of preemption. The theory asserts the importance of using information to make sound judgment about national issues like public healht and drug-related regulations (Deftos, 2008; Glantz & Annas, 2008). The three findings indicated that information about adverse drug effects were significant in ADRs research and lessening adverse drug effects and incidence of ADRs.

The findings of this study helped advanced research methodology in the field of pharmacovigilance. The findings of this study revealed perceptions about effectiveness and limitations of FAERS and the Sentinel Initiative. The findings of this study indicated that qualitative methodology was also effective in comparing the benefits and challenges of surveillance methodology associated with FDA's Sentinel Initiative compared to FAERS. The findings of the study also added to the current research base regarding pharmacovigilance systems.

Ultimately, the results of the study increased awareness of advantages and disadvantages of the FAERS and the Sentinel Initiative. Information from the data provided information regarding the effectiveness of the FAERS and the Sentinel Initiative. At this point, the Sentinel Initiative complements the FAERS system and it does not replace FAERS system as it currently stands. The Sentinel Initiative only aims to provide additional information on adverse drug events. The results of the study could increase the public knowledge of the reporting systems used by the FDA to control ADRs.

The insights from this study could support the FDA's efforts to improve reporting systems effectiveness to detect ADRs. The benefits and challenges of both FAERS and the Sentinel systems found in this study could serve to be foundations for further improvements to the programs. The presence of FAERS and Sentinel Initiative improved the vigilance of the public towards the adverse effects of drugs. Availability of FAERS and Sentinel Initiative also improved drug safety. FAERS and Sentinel Initiative provided a systematic database, which included health data, that could be used to improve public

health. As such, they must also be improved. Improvement of these programs would lead to improvement of health and quality of life of the public because challenges of the programs on ADR generation would be identified for ease of addressing them.

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Social Significance

This research definitely had potential to increase awareness of advantages and disadvantages of the FAERS and the Sentinel Initiative. It was expected that the data would provide information regarding the effectiveness of the FAERS and the Sentinel Initiative. This study would increase the public knowledge of the reporting systems used by the FDA to control ADRs. The lessons learned from this study could support the FDA's efforts to improve reporting systems effectiveness to detect ADRs. This research would also add to the research base regarding pharmacovigilance systems. Moreover, with the findings of the study, the benefits and challenges of both FAERS and the Sentinel systems would determine that would serve as basis for further improvements to the programs. Through this, health and quality of life of consumers would be improved because the challenges of the programs on ADR generation would be identified for ease of addressing them. As a result, safer medications would be available in the market for consumers due to availability of huge safety data through the sentinel system which would improve health and quality of life for patients.

The findings of this study helped in providing support for surveillance systems such as FAERS and Sentinel Initiative. These systems monitored the adverse reactions to drugs and medication. Monitoring the adverse reactions added to the information

available to the public domain. Both the public and the patients benefitted from the surveillance systems. Due to these systems, thousands of lives of people were saved. This chapter concludes the study.

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Summary and Conclusions

Occurrence of ADRs in the U.S. have increased in the past decade. ADRs were costly and had a negative impact on public health programs (Yadav, 2009). Moreover, ADRs were among the leading causes of death in many countries, including the United States. From 2004 to 2012, men and women both reported 60,000 deaths due to ADRs (Keating & Millman, 2014). Pharmacovigilance systems such as FAERS and Sentinel Initiative were used to detect and prevent ADRs. The purpose of this comparative case study of the FDA Adverse Events Reporting System (FAERS) surveillance system and the FDA's Sentinel Initiative was to determine the benefits and consequences of the Sentinel Initiative in terms of drug consumer's safety.

The theory of preemption assumes that it is important to use information to make sound judgment regarding issues or activities of national importance, such as prescription drug-related regulations, require uniform federal regulation, which cannot be provided by states (Deftos, 2008; Glantz & Annas, 2008). Given this assumption together with the existing literature, it was expected that there will be differences with FAERS and Sentinel Initiative programs and that it promoted pharmacovigilance activities.

Three themes emerged from the data analysis:

- **Theme 1.** The presence of FAERS and Sentinel Initiative improved the vigilance of the public towards the adverse effects of drugs and promotes health and public safety.
- **Theme 2.** FAERS and Sentinel Initiative provided a systematic data collection for a database that would use health data to improve public health.
- **Theme 3.** The reporting model provided a regulatory mechanism after the drug approval activities in order to evaluate the medicinal products.

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Appendix A: Invitation Letter

Dear _____:

Good day!

My name is Sonia Batra. I am a doctoral student at Walden University's PhD Public Health program. I am currently conducting my dissertation research on the use of the FDA Adverse Events Reporting System (FAERS) and the Sentinel Initiative in an effort to compare the two and determine the benefits and challenges associated to these said programs. You are seleceted to participate in the study because you are identified as a subject matter expert in the field of pharmacovigilance and are familiar with FDA Adverse Event Reporting System (FAERS) and the FDA sentinel initiative. I would like to invite you to participate in a key informant interview that will last approximately 45 minutes. The information that you can provide will be helpful in fulfilling the purpose and significance of this study, and help improve the current state of pharmacovigilance systems in the country.

Please be informed that your participation is protected under the ethical rules and considerations imposed by the IRB to ensure that you are aware of your rights as participants to this study. Please also note you will not receive any payment (thank you gifts, compensation, or reimbursement (for travel costs, etc.)) for participating in the research study. Should you wish to participate in this study, you may reply to signify your interest to participate. I will then send you a copy of the informed consent, which will need to be signed and returned to me via email or fax once you have finalized your

decision to participate. Additionally, the informed consent may be returned to me in person if we are having face to face interview.

Thank you very much.

Sincerely,

Sonia Batra

Appendix B: Informed Consent

The purposes of this form are to provide you, as the potential participant of this study, with the relevant information that may affect your decision as to whether or not to participate in this research and to record the consent of those who agree to be involved in the study.

You are seleceted to participate in the study because you are identified as a subject matter expert in the field of pharmacovigilance and are familiar with FDA Adverse Event Reporting System (FAERS).

STUDY PURPOSE

The purpose of the present study of the FAERS surveillance system and the FDA's Sentinel Initiative is to determine the benefits and consequences of the Sentinel Initiative in terms of drug consumer safety.

DESCRIPTION OF RESEARCH STUDY

If you decide to participate, you will join a study involving telephone/face to face interviews which will be recoded. If you say YES, then your participation will last for approximately 45 minutes. Twenty subjects will be invited to participate in this study.

REQUIRED LANGUAGE: English

RISKS

There are minimal risks associated with participating in the study.

BENEFITS

Although there may be no direct benefits to you, the possible benefits of your participation in the research are to identify benefits and challenges associated with FAERS and the Sentinel Initiative to serve as basis for improvement of the programs.

NEW INFORMATION

If the researcher finds new information during the study, the information would be shared with you and you will have an option to change your decision about participating.

CONFIDENTIALITY

All information obtained in this study is strictly confidential. The results of this research study may be used in reports, presentations, and publications, but the researcher will not identify you. In order to maintain confidentiality of your records, Sonia Batra will use pseudonyms to replace the name or identification of each subject. Any paper copies will be kept in a locked cabinet and electronic formats will be protected by a password. Once the study is completed and accepted by Walden University, all digital recordings will be deleted.

WITHDRAWL PRIVILEGE

Participation in this study is completely voluntary. It is ok for you to say no, and you will not incur any consequences for it. Even if you say yes now, you are still free to say no later, and withdraw from the study at any time. If you should withdraw from the study, any digital recordings will be deleted.

Please also note you will not receive any payment (thank you gifts, compensation, or reimbursement (for travel costs, etc.)) for participating in the research study.

VOLUNTARY CONSENT

Any questions you have concerning the research study or your participation in the study, before or after your consent, will be answered by Sonia Batra.

This form explains the nature, demands, benefits and any risk of the project. By signing this form, you agree knowingly to assume any risks involved. Remember, your participation is voluntary. You may choose not to participate or to withdraw your consent and discontinue participation at any time without penalty or loss of benefit. In signing this consent form, you are not waiving any legal claims, rights, or remedies. A copy of this consent form will be given (offered) to you.

Please feel free to contact me at xxx-xxx-xxxx for concerns regarding the interview or if you have any other questions regarding the study. My email address is Xxxx@xxxx.com.

You can also contact Walden university's Research Participant Advocate (USA number 001-612-312-1210 or email address irb@waldenu.edu) if you have any question regarding your rights as a participant.

Your signature below indicates that you consent to participate in the above study

_____	_____	_____
Participant's Signature	Printed Name	Date

Appendix C. Interview Guide

Introduction

- Greet participant. Introduce the study and its purpose

The interview is being conducted to determine the benefits and consequences of the Sentinel Initiative in terms of drug consumer safety. This is a qualitative study focusing on your perceptions beause you have worked closely with FAERS program and are aware of the Sentinel Initiative.

- Review Informed Consent
- Provide flow of the interview

Below are the semi-structured interview questions that will be asked during the interview:

1. How does the Sentinel Initiative improve data gathering of adverse drug reactions compared to FAERS?
    a. What are the methods does the Sentinel Initiative use to improve data gathering of adverse drug reactions compared to FAERS?
    b. Who is responsible to implement and evaluate such methods?
    c. What are potential challenges or risks that you perceive from these methods?
        i. Why?
        ii. Can you tell me more about that?
    d. What are potential benefits from these methods?
        i. Why?
        ii. Can you tell me more about that?
2. How does the Sentinel Initiative address underreporting of adverse drug reactions compared to FAERS?

   a. What are the methods that the Sentinel Initiative uses to address underreporting of adverse drug reactions compared to FAERS?
   b. Who is responsible to implement and evaluate such methods?
   c. What are potential challenges from these methods?
      i. Why?
      ii. Can you tell me more about that?
   d. What are potential benefits from these methods?
      i. Why?
      ii. Can you tell me more about that?

3. How does the Sentinel Initiative address differential reporting of adverse drug reactions compared to FAERS?
   a. What are the methods for the Sentinel Initiative uses to address differential reporting of adverse drug reactions compared to FAERS?
   b. Who is responsible to implement and evaluate such methods?
   c. What are potential challenges from these methods?
      i. Why?
      ii. Can you tell me more about that?
   d. What are potential benefits from these methods?
      i. Why?
      ii. Can you tell me more about that?

4. How does the Sentinel Initiative address uneven quality of adverse drug reactions reports compared to FAERS?
   a. What does the Sentinel Initiative address uneven quality of adverse drug reactions compared to FAERS?
   b. Who is responsible to implement and evaluate such methods?

c. What are potential challenges from these methods?
    i. Why?
    ii. Can you tell me more about that?
d. What are potential benefits from these methods?
    i. Why?
    ii. Can you tell me more about that?

5. What are the possible strategies that limit the disadvantages/challenges of the Sentinel Initiative in terms of its impact users?
    a. Who is responsible to implement and evaluate such strategies?
    b. What are potential challenges from such strategies?
    c. What are potential challenges from these methods?
        i. Why?
        ii. Can you tell me more about that?
    d. What are potential benefits from these methods?
        i. Why?
        ii. Can you tell me more about that?
    e. Is there anything else you want to tell me about ADR surveillance?
        i. Why?
        ii. Can you tell me more about that?
    f. Can you recommend another key informant who may be interested in participating in my study?
        i. Why?
        ii. Can you tell me more about that?

Appendix D. Emerging Codes

Code	**Meaning**	**Quotes from Participants- Supporting Code**
Data collection	FAERS and Sentinel collect data from patients regarding the adverse effects of drugs.	The availability of vast volume of data which includes not only the drug reaction details but also the information such as medical history of the patient, personal details such as age etc. also all this information will help us derive relevant and durable information from the data. (Participant 17)
Use of health data	Health data is used for the record of FDA.	There are various organizations and to be exact I believe 18 organizations that are involved in retrieving health data. (Participant14)
Active system	The Sentinel Initiative is an active system of reporting.	So benefits like I told you that it's an active system they have immediate results. (Participant 4)
Voluntary reporting	The voluntariness of reporting is evident in the regulation.	FAERS is basically everything is voluntarily done most of the time it is more specific to particular patients. (Participant 1)
Systematic database	Reporting the adverse drug reactions allow having a present systematic database.	FAERS is the FDA adverse events reporting system. It's a database that contains the information on Adverse events (AE's) and medication errors. (Participant 7)
Privacy	Privacy of the individuals who report adverse effects might be at stake.	I really see here is the privacy issue. The HIPAA compliance. I don't know if the patients would like to share their information to a third party. (Participant 6)
Relative assessment	There can be differences in how a person assesses or evaluates the effects of drugs.	With the FAERS system addressing adverse differential FAERS is dependent on whether the patient really calls FDA or health care company and that one is limited. Whereas with Sentinel the patient may be either talking to healthcare profession that I had reaction with drug and it might get reported much more better than the FAERS system where the patient might

Code	Meaning	Quotes from Participants- Supporting Code
		even not know where to report. (Participant 8)
Unexpected adverse effects	The unexpected adverse effects of drugs should be reported in order to be prevented.	There would be more clinical information available regarding the adverse effect and what was happening so that would be one major benefit. (Participant 12)
Threats to public health	The adverse effects of drugs pose threats to public health.	I say society it means all the players who are responsible for managing healthcare in the system. (Participant 2)
Health safety	Health safety of patients can be achieved if drugs are safe.	The potential benefits of the patients ultimately the FDA was created to benefit the patients and consumers and the larger population will be benefited by this and more genotyping & genomics data. (Participant 2)
Patient-centeredness	FAERS and Sentinel Initiative are focused on the welfare of patients.	I think it's mostly patients safety, they are having a lot of information sharing it they are able to share it, they are compiling they are getting a great deal more info on all these products hopefully to be used for a patient safety. (Participant 20)
Coincidental occurrences	Coincidental occurrences on patients that do not have direct correlation to the drugs might be mistaken as adverse drug effects.	I can confirm it if you like all the adverse reactions that happened whether it was on doctors clinic or it happened anywhere else in the hospital only 6-10% were reported since the institution established FAERS whereas the sentinel program because it is not asking you report anything it is asking you to just keep your data in a particular format (Participant 2)
Risk evaluation	The risks on drugs will properly be assessed if there is a proper reporting model.	I think the challenges are that you know with a lot of data you also comes with it is noise and you know the quality of data and probably you can have where signals will get lost and then you have different interpretations of signals of

Code	Meaning	Quotes from Participants- Supporting Code
		what is actually a risk and what is I think it gets a little bit murky with that large amount of data (Participant).
Reporting model	The reporting model of how adverse drug effects are recorded should be systematic.	It doesn't seem that they have a separate method they can use to overcome under reporting of worst events so if the data is not there they can obtain any additional information. (Participant 5)
Post-drug approval activities	Post-drug approval activities must be evaluated to ensure the safety of the public.	So basically they use all these query methods so that they can query these large database to determine to get the desired results of what are on what features are they looking for and what kind of problems they want to solve or especially what drug they want to improve. (Participant 4)
Evaluation of products	The proper evaluation of products should be the priority in order to ensure health safety.	Evaluation is done principally by FDA and they will be the one who will analyze the data and gather critical information out of this. (Participant 18)
Responsibility	There should be a government agency that regulates drugs in order to monitor responsibility on the safety of drugs.	So here again I think the agency has the ultimate responsibility when it comes to reporting though in general it is on … it's on the health care professionals and consumers. (Participant 20)
Accountability	There should be a government agency that regulates drugs in order to monitor accountability on the safety of drugs.	Again the FDA, the stakeholders are solely responsible for implementing and evaluating these methods. (Participant 17)
Preventive action	The reporting model is a form of preventive action to ensure that future similar incidents will be prevented.	I think there are may be 18 organizations collecting this data help data warehousing and ensure companies like that have access to vast of data and vast of health data. (Participant 13)
Alerting the public	The public has the right to know on the possible adverse drug	The potential challenges which I am looking upon in this under reporting of adverse from these methods is to instill

Code	Meaning	Quotes from Participants- Supporting Code
	effects based on the experience of others.	a sense of security amongst the patients and we have to educate them that their personal data is only used for medicinal and research purposes. (Participant 17)
Evidence-based	The reporting of adverse drug effects by the patients will allow evidence-based conclusions.	Doctor must have prescribed something and there must be some evidence and records they don't have to wait for many years. (Participant 19)
Vigilance	Vigilance in the pharmaceutical industry must be improved.	I mean all the stake holders that are involved should be responsible whether be the manufacturers or the distributors or the FDA or the healthcare professionals or even the patient. (Participant 16)
Accessibility	The records and data collected should be made accessible to the public.	Information is generally documented within the healthcare providers database it's more readily accessible to FDA to perform to better evaluate the data. (Participant 16)
Inclusive	A more inclusive system should be created so that the development will go beyond research purposes.	To obtain extensive stakeholders and partners to participate in this imitative there will have to some kind of method to educate consumer for this work so that they may be able to share their health care info to the database. (Participant 5)
Discovery of new risks	New risks on the adverse drug effects will be prevented.	That it can eliminate under reporting to extent but it will be still be there because the access to data is small and I think they are also working on it once data bases are linked and they have access to those databases then they will have better analysis to problems of adverse drug reactions. (Participant 4)
Other stakeholders	A more inclusive progress in the field of pharmacovigilance is possible if there are more stakeholders.	Consumer may not allow releasing their health care info and they need to increase their stakeholders if they want to expand and implement all over the country. (Participant 5)

Code	Meaning	Quotes from Participants- Supporting Code
Drug safety	Drug safety should be prioritized in ensuring that there are proper reportorial mechanisms.	It will help derive the FDA and to evaluate about a drug and take some safety measures about a drug. (Participant 17)
Opportunity to improve healthcare professionals	Healthcare professionals will improve their performance if the drugs are properly regulated.	So the challenge again would be the lack of partnership, they have to increase their partnership to all physicians, pharmacies in order to expand their data base. (Participant 5)
Disease occurrence	Disease occurrence can be lessened if there is proper regulation of drugs available in the market.	There are some other diseases and other things that I have and if I am going to take this medication it going to have an impact on me. (Participant 19)

Appendix E. Emerging Themes

Themes	**Total No. of Responses**	**Associated Codes and Categories**
Theme 1. The presence of FAERS and Sentinel Initiative improves the vigilance of the public towards the adverse effects of drugs and promotes health and public safety.	52	Patient's Health (Total: 15) Unexpected adverse effects (4) Threats to public health (4) Patient-centeredness (3) Health safety (2) Coincidental occurrences (2) Preventive Measure (Total: 12) Vigilance (4) Preventive action (3) Alerting the public (3) Evidence-based (2) Drug Manufacture (Total: 12) Drug safety (6) Opportunity to improve healthcare (3) professionals Disease occurrence (3) Other Stakeholders (Total: 13) Other stakeholders (5) Accessibility (3) Inclusive (3) Discovery of new risks (2)
Theme 2. FAERS and Sentinel Initiative provide a systematic data collection for a database that would use health data to improve public health.	28	Data Collection (Total: 28) Systematic database (7) Privacy (4) Voluntary reporting (4) Data collection (4) Active system (4) Use of health data (3) Relative assessment (2)
Theme 3. The reporting model provides a regulatory mechanism after the drug approval activities in order to evaluate the medicinal	22	Regulatory Mechanism (Total: 22) Accountability (6) Reporting model (4) Post-drug approval activities (4)

products.		Risk evaluation (3) Evaluation of products (3) Responsibility (2)