

HARMONIZED PHARMACOVIGILANCE PRACTICES
A PATHWAY TO SAFER PHARMACEUTICALS IN A GLOBALIZED INDUSTRY

by

SAMANTHA MAGAZU

(Under the Direction of David Mullis)

ABSTRACT

Pharmacovigilance practices have focused on the reporting of adverse drug reactions to medicinal products. In an increasingly global industry, attempts have been made to harmonize pharmacovigilance practices internationally in order to advance the knowledge of a medicine's safety profile and to ensure that new information is both identified as quickly as possible and communicated to all those potentially impacted. While pharmacovigilance has evolved in recent years, there still remain areas of disharmony in international practices. This thesis compared the pharmacovigilance legislation in the United States with that of the European Union in order to establish what areas of current legislation were harmonized between the regions. Comparisons were also made between the health authorities' requirements and the recommendations of international organizations. By establishing where disharmony exists, efforts can more efficiently address strategies to create a pharmacovigilance system that can be implemented internationally, thus promoting the safer use of medicines.

INDEX WORDS: Pharmacovigilance, Drug Safety, Harmonization

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SAMANTHA MAGAZU

B.A., The University of Vermont, 2006

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment
of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2013

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SAMANTHA MAGAZU

Major Professor: David Mullis

Committee: Paul Brooks
Randall Tackett

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
December 2013

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CHAPTER 1 – INTRODUCTION

What is Pharmacovigilance?

The World Health Organization (WHO) defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.”¹ The thalidomide disaster of 1961 initiated the international effort to address drug safety issues worldwide. Early pharmacovigilance activities included reactive techniques to respond to risks associated with medicines once they had been placed on the market. In recent years, the scope of pharmacovigilance has expanded in response to changing global pharmaceutical industries, increased access to medicines, varied utilization of medicines and new, more powerful tools and databases for tracking and analyzing data; however, the discipline needs to develop further to meet the needs of the 21st century public health systems and consumer expectations.

Thalidomide was first marketed in 1957 and was widely prescribed in Europe, Australia, Asia, Africa and the Americas. In the early 1960s, thalidomide was found to be associated with severe birth defects in children born of mothers who had been prescribed thalidomide during pregnancy. More than 10,000 cases of birth defects were reported in over 46 nations and included children born with missing or abnormal limbs, spinal cord defects, cleft lip or palate, absent or abnormal ears, heart, kidney and genital abnormalities and abnormal formation of the digestive system. Approximately 40% of thalidomide victims died within a year of birth. In 1961, thalidomide was taken off the market in many countries.²

The development of spontaneous reporting systems around the world came as a result of new regulations put in place after the thalidomide tragedy of the 1960s. The WHO International Programme for Adverse Reaction Monitoring was set up in order to identify rare adverse drug reactions (ADRs) that could not be identified through the limited scope of clinical trials. Adverse events initially were reported through the British Yellow Card system and the Food and Drug Administration's (FDA) Form 1639. Since then, pharmacovigilance practices have moved toward a more proactive approach, where the safety of medicines is studied and tracked from the earliest stages of development through the entire product lifecycle including post-marketing.

The largest source of safety information remains reports of adverse drug reactions. The basis of most existing pharmacovigilance systems is adverse drug reporting, which extends throughout the entire product lifecycle from the earliest developmental phases through post marketing safety monitoring. Adverse event reporting is required in the pre-marketing clinical trials, while spontaneous reports and reports from post-marketing studies are used to identify rare adverse effects that could not be identified during the clinical trial program as well as for signal detection. The stages of clinical development of medicines are shown in Figure 1. In each stage, safety is explicitly considered.

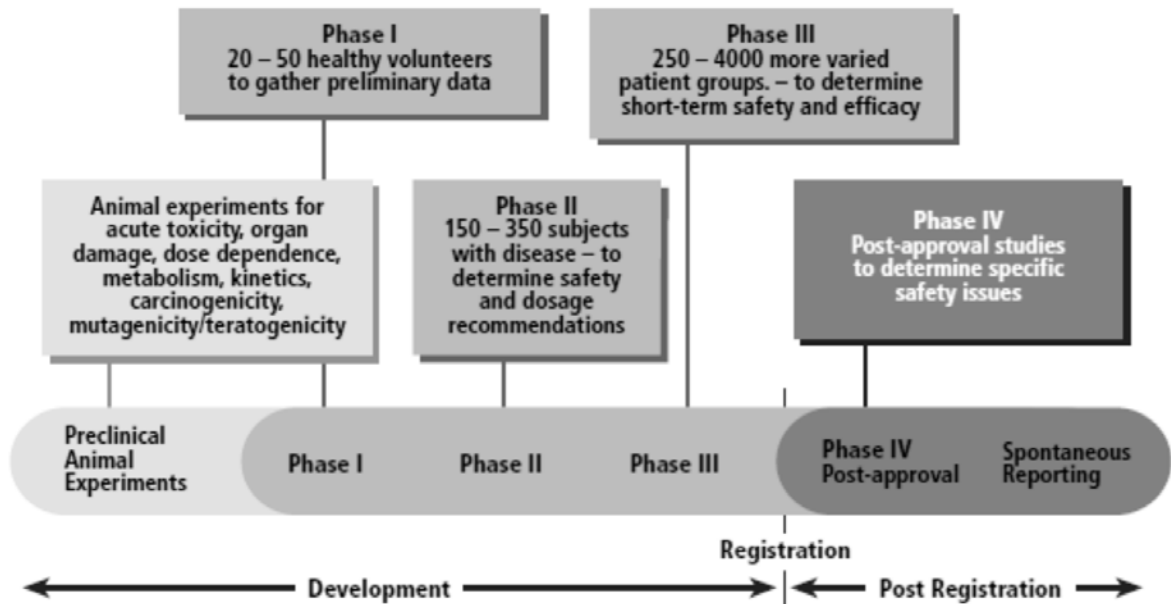


Figure 1: Clinical Development of Medicines³

Initiatives by the Council for International Organizations of Medical Sciences (CIOMS) and by the International Conference on Harmonization (ICH) moved pharmacovigilance in the direction of risk management. Risk management is achieved through the systematic discovery and communication of the specific known and unknown risks of a medicine as well as the plan to address and minimize those risks and unknowns. Pharmacovigilance is now seen as a “living” entity where data are continuously gathered and communicated in order to allow for the adaptation of fluid strategies for addressing adverse effects and other drug-related problems. These initiatives demonstrate a clear understanding by both industry and regulators that pharmacovigilance must be seen as more than simply adverse event reporting. The technologies behind the medicines used today and the ways that those medicines are accessed and used continue to evolve and expand, creating new demands on the discipline of pharmacovigilance. The regulations, systems and tools used to monitor the safety of drugs and protect public health have not met those demands.

Tsintis and La Mache stated that, “despite the establishment of pharmacovigilance systems on a global basis, adverse drug reactions still remain a major worldwide cause of morbidity and mortality. It was estimated in 1994 that such reactions accounted for more than 100,000 deaths, the fourth largest cause of deaths in the United States.”⁴ Challenges continue to arise from an increasingly globalized world where drugs are available across borders and an increasing number of people are exposed to medicines. The Internet provides a place where medicines can be bought and sold, increasing self-medication and abuse. A general lack of knowledge of drug interactions and medication errors also exists. New technologies create complex medicines of which little is known while simultaneously creating tools for risk management and protection of consumers. Each of these challenges poses a new role for pharmacovigilance – requiring an expansion from monitoring and assessing adverse drug reactions to a system more closely linked to patterns of drug use and communication patterns within individual societies and worldwide.

Pharmacovigilance Legislation

U.S. Pharmacovigilance Legislation

The first drug safety regulations in the United States were a direct result of the thalidomide disaster. The FDA’s authority to approve and monitor drugs lies in the Federal Food, Drug and Cosmetic (FD&C) Act⁵. The 1962 Kefauver-Harris Drug Amendments to the Act were passed to ensure drug efficacy and greater drug safety. At the 50th Anniversary of the 1962 Drug Amendments, FDA Commissioner Margaret Hamburg noted that “while the 1938 FD&C Act completely reformed the public health system by greatly expanding FDA’s responsibilities and powers, it had serious shortcomings that stymied consumer protection.”⁶ In 1970, the first patient package insert was required by the FDA to inform the patient about specific risks and benefits of oral contraceptives.⁷ The Prescription Drug User Fee Act (PDUFA III) was reauthorized in 2002

and included goals for the FDA to produce guidance documents on risk management activities.⁸ After a number of key safety issues for certain drugs were revealed in a post-approval environment, the FDA began a formal process for evaluating its drug safety evaluation processes. In 2004, CDER was charged with the task of creating a committee to study the effectiveness of the U.S. drug safety system, with an emphasis on the post-market phase.⁹ As a result of the recommendations of that committee, the Drug Safety Board was announced in 2005 to advise the CDER on drug safety issues and work with the agency in communicating information to healthcare professional and patients.⁶ In 2007, the Food and Drug Administration Amendments Act (FDAAA)¹⁰ was passed, which greatly revised the regulations governing the FDA's responsibilities including a wide array of new authorities in drug safety. The FDAAA was implemented through a number of enhancements to the FDA's drug safety program, including:

- New capabilities for detecting and responding quickly to drug safety issues that emerge after marketing;
- Enhanced quality, speed, and transparency of the FDA's decisions about how to address specific drug safety issues;
- Earlier and more effective drug safety communication to the public; and
- Stronger protection of patients from preventable medication errors.¹¹

The FDAAA granted the FDA the authority to require manufacturer's to conduct postmarketing safety studies and clinical trials, to require a change in a drug's label based on new safety information, to require manufacturers to implement special risk management programs, called risk evaluation and mitigation strategies (REMS) when deemed necessary by FDA, and to post quarterly online reports of adverse event data.¹⁰

European Pharmacovigilance Legislation

As in the U.S., the first real efforts and systems to collect adverse event data were put into place as a direct result of the thalidomide disaster. By the early 2000s, European regulators were undertaking a systematic review of their drug safety programs with the goal of making improvements. In December 2010, new pharmacovigilance legislation, referred to as the 2010 Pharmacovigilance Legislation, was adopted in the EU with the aim of reducing the number of adverse drug reactions.¹² This legislation is found in Directive 2010/84/EU, which amended 2001/83/EC and Regulation (EU) No 1235/2010, which amended Regulation (EC) No 726/2004. Most of the legislation has been effective since July 2012. Key impacts of the 2010

Pharmacovigilance Legislation include:

- Adverse drug reaction reports are reported by the marketing authorization holder (MAH) only through EudraVigilance and not to individual competent authorities
- Periodic Safety Update Reports (PSURs) are no longer required for products considered low risk or with established safety profiles, unless new concerns arise
- PSURs are to be submitted electronically through an E.U. repository to the European Medicines Agency (EMA)
- Strengthened legal basis for requiring post-authorisation safety and efficacy studies (PASSs and PAESs) from MAHs
- Requirement of Risk Management Systems for all new medicines
- Requirement for MAHs to maintain a Pharmacovigilance System Master File (PSMF), available for inspection by competent authorities, in place of the Detailed Description of the Pharmacovigilance System (DDPS) that was previously required for marketing approval applications

- Requirement to submit specific product information electronically to the EMA and to maintain the information¹³

Adverse Drug Reaction Reporting Databases

MedWatch and the FDA Adverse Event Reporting System (FAERS)

In the U.S., safety information and adverse events are reported through the MedWatch program. MedWatch was launched in 1993 by FDA Commissioner David Kessler who recognized that a mechanism for collaboration with doctors, nurses and pharmacists and the FDA was needed for achieving identification and evaluation of serious adverse events and product quality issues. The program is voluntary and receives over 40,000 reports directly from physicians and patients.¹⁴ In addition, manufacturers send in hundreds of thousands of reports to the FDA that clinicians report to them. This accumulation of reports often leads to the discovery of new safety data, which can be disseminated and retrieved by the FDA, healthcare professionals, patients and industry representatives over the Internet. In an “expert column” published by Medscape, Norman Marks, MD, Director of the FDA’s MedWatch program, wrote “The FDA’s goal is to deliver targeted, product-specific and actionable information to both providers and their patients, ideally at the point-of-care, so that this information can be considered in the shared decision-making about both therapeutic and diagnostic measures.”¹⁴

The database used by the FDA for storing and evaluating adverse events and medication errors associated with medicinal products and biologics is called the FDA Adverse Event Reporting System (FAERS). FAERS is used to identify signals of potential safety concerns. Healthcare professional and consumers can voluntarily report adverse events to the FDA, while manufacturers are required to report. All reports received are entered into FAERS.¹⁵

EudraVigilance

In the European Union, EudraVigilance serves as a data processing network and management system for reporting and evaluating adverse drug reactions. First launched in 2001, and similar to the FDA's MedWatch program, EudraVigilance allows for the electronic exchange of adverse drug reaction reports between the European Medicines Agency (EMA), National Competent Authorities and manufacturers. The reports lead to the detection of safety signals. Since November 20th, 2005, electronic reporting of suspected serious adverse reactions has become mandatory through the EudraVigilance system. There are two modules for EudraVigilance: The EudraVigilance Clinical Trial Module (EVCTM) and the EudraVigilance Post-Authorisation Module (EVPM).¹⁶

Prior to the 2010 Pharmacovigilance Legislation, sponsors of clinical trials and Marketing Authorisation Holders (MAHs) were required not only to report adverse events through EudraVigilance, but also individually to the competent authorities at a national level. Requirements between nations varied in both reporting requirement and formats, with some countries requiring paper submissions and others electronic, or some countries requiring translation of reports to local languages with others accepting English language reports.

Vigibase

While the MedWatch and EudraVigilance programs monitor drug safety at a more localized level in the U.S. and E.U. respectively, the WHO Programme on International Drug Monitoring in Uppsala, maintains the international database, called VigiBase, of adverse drug reactions, serving the national pharmacovigilance centers that are associated with the WHO

program. National centers submit approximately 150,000 reports to the Uppsala Monitoring Centre (UMC) every year. Like the MedWatch and EudraVigilance programs, the UMC strives to not only collect and analyze drug safety information at an international level, but also to disseminate that information to help develop and maintain scientific expertise on drug safety.¹⁷ Reporting is done electronically, and most national centers have direct access to the data stored in the UMC databases.

Risk Management

While spontaneous reporting and clinical trial adverse event reporting have become well established in pharmacovigilance practices and systems have been developed, put into place and refined, it is not without flaws, as outlined above, as a tool toward safer medicines. Adverse event reporting was created as a response to safety issues – it is a reactive approach. Risk management, however, has emerged as a preventative tool in pharmacovigilance. Risk management strategies provide a method for continuously studying the benefit-risk profile.²

The FDA defines risk management as “an iterative process of (1) assessing a product’s benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance.”¹⁸ Risk management is the combination of risk assessment and risk minimization. Risk assessment is an evidence-based evaluation of a product’s risks that begins during development and continues through the product lifecycle through marketing. The risks are examined in relation to the benefits. Once risks are defined, the tools that can be used to minimize those risks can be determined (risk minimization). The continuous monitoring and assessment of risks means that tools will develop over time and change as the knowledge of the

product’s safety is better understood. Risk management also fills the void that exists in the knowledge of the true safety information of a product at the time of market approval.

The concept of risk management also exists in the pharmacovigilance legislation and guidance documents in the European Union (EU). While there is no internationally agreed upon definition for risk management, the basic concepts and tools used in its implementation do overlap. International groups such as CIOMS and ICH do currently have initiatives working toward a more harmonized understanding of risk management as will be discussed in the next chapter. The table below compares the basic processes and concepts of risk management in the U.S. and EU.

Table 1: Concepts of Risk Management

FDA’s Process of Continuous Monitoring of Risk Information	EMA Approach to Risk Management
<ul style="list-style-type: none"> • Evaluating benefits and risks 	<ul style="list-style-type: none"> • Risk detection
<ul style="list-style-type: none"> • Minimizing risks through appropriate interventions 	<ul style="list-style-type: none"> • Risk assessment
<ul style="list-style-type: none"> • Evaluating such interventions as new knowledge is gathered 	<ul style="list-style-type: none"> • Risk minimization
<ul style="list-style-type: none"> • Revising such interventions accordingly 	<ul style="list-style-type: none"> • Risk communication

The concept that all of the information on the safety of a product cannot be fully recognized through the clinical trial program is also seen in the European guidance documents. *The Good Pharmacovigilance Practices (GVP) Module V - Risk management systems* states: “It is recognised that at the time of authorization, information on the safety of a medicinal product is relatively limited. This is due to many factors including the relatively small numbers of subjects in clinical trials compared with the intended treatment population, restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co-medication, restricted

conditions of use, relatively short duration of exposure and follow-up, and the statistical problems associated with looking at multiple outcomes.”¹⁹

The FDA recommends, and requires in some cases, the use of Risk Minimization Action Plans (RiskMAPs) for those products where routine risk management strategies (labeling and postmarketing trials) are not sufficient. RiskMAPs are a type of safety program based on specific goals and objectives for minimizing risks. Each RiskMAP can target one safety issue, or multiple concerns with selective tools. The RiskMAP guidance⁸ acknowledges that while manufacturers should incorporate risk management into their pharmacovigilance systems, not all products require the formalized processes and documentation of a RiskMAP.

Since implementation of the 2010 Pharmacovigilance Legislation in the EU, risk management plans, which incorporate the same principles of risk assessment to determine the need for and specific tools to be used in risk minimization as described by the FDA, are required as part of a Marketing Authorisation Application (MAA). The Risk Management Plan contains much of the same content that the FDA requires in RiskMAPs but, again, is required for all products marketed in the EU while RiskMAPs are required in the U.S. only for those products with more significant risks. The EudraVigilance database of adverse events now serves as a central tool for risk detection as part of the risk management plan.

Establishing a State of Harmonization

The recent efforts to shift the focus of pharmacovigilance toward a more proactive approach and to establish pharmacovigilance practices that can be implemented globally, demonstrate a recognition that harmonized pharmacovigilance practices are required to meet the needs of the various stakeholders in pharmacovigilance, including health authorities, the pharmaceutical industry, healthcare professionals and consumers. In addition, harmonization

would also promote the safer use of medicines and aid in the global mission for public health. The practices of a particular region are directly correlated to the pharmacovigilance legislation that exists in that region. By defining the requirements and practices, pharmacovigilance legislation defines the safety information that is known about medicinal products and the processes that are available to management risks. In an effort to establish the outcome of the recent attempts at harmonizing pharmacovigilance practices, this thesis directly compared the pharmacovigilance legislation of the U.S. and EU to identify areas where disharmony still exists.

CHAPTER 2 - INTERNATIONAL HARMONIZATION EFFORTS

While the legislation governing and practices behind pharmacovigilance have progressed in recent years, the need for an internationally harmonized system still exists. Differences in practices mean that rates and quality of adverse reaction reporting and risk management policies vary among countries. When drug safety reporting requirements differ among health authorities, different sets of data become available in different regions. When risk management is implemented in inconsistent ways, information known about the safety of medicines and the ability to manage new safety information remains isolated and varying. These inconsistencies lead to a disparity and disjunction between what is known about the safety of a medicine as well as what medicines are available in different parts of the world. The goal of harmonization has always been to protect public health. The pharmaceutical industry shares responsibility in the communication of drug safety information, which would be enhanced by a global system that allows manufacturers to communicate new safety information to regulatory agencies in all countries where the drug concerned is marketed. In addition, regulatory agencies should have harmonized standards, requirements and practices for dealing with emerging safety issues and public safety concerns. An agreed-upon understanding of what is a safety concern versus a crisis and what is required for reporting of safety information between industry and regulators would minimize miscommunications and allow for greater worldwide drug safety and utilization. International organizations have shifted from developing guidelines and systems for gathering safety data on medicines to a focus on a worldwide pharmacovigilance system with a unified approach to drug safety. The three most influential international groups – The World Health

Organisation (WHO), The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and The Council for International Organizations of Medical Sciences (CIOMS) - and their efforts towards harmonization of pharmaceutical regulation specific to pharmacovigilance and other efforts towards safer medicines will be discussed.

The World Health Organisation (WHO)

Since 1948, WHO has been an international organization striving to improve public health worldwide. WHO has been an influential resource for regulatory authorities and other industry organizations helping to define priorities for public health and has created programs to help meet those priorities.²⁰ On its website, WHO defines its core functions as:

- providing leadership on matters critical to health and engaging in partnerships where joint action is needed;
- shaping the research agenda and stimulating the generation, translation and dissemination of valuable knowledge;
- setting norms and standards and promoting and monitoring their implementation;
- articulating ethical and evidence-based policy options
- providing technical support, catalyzing change, and building sustainable institutional capacity; and
- monitoring the health situation and assessing health trends.²⁰

Medicines and health products is just one category of the vast number of programs and projects that WHO is involved in to fulfill its functions and goals. Within the category of medicines and health products, there are five technical areas – Medicines Policy, Governance and Country Collaboration, Quality Assurance and Safety: Medicines, Medicine Access and Rational Use,

Medical Devices and Diagnostics and Quality, Safety & Standards: Vaccines. These technical areas serve WHO's vision that "people everywhere have access to the essential medicines and health products they need; that the medicines and health products are safe, effective and of assured quality; and that medicines are prescribed and used rationally."²⁰

Based on the belief that the safety of medicines is a global responsibility WHO created the Medicines Safety Team to develop norms and standards for pharmacovigilance, promote information exchange on medicines safety, provide country support, fundraise for pharmacovigilance activities and collaborate with various stakeholders.²⁰ The Medicines Safety Team contributes to the area of pharmacovigilance through WHO-approved national pharmacovigilance centers, hosting events related to pharmacovigilance, serving as an advisory body, studying drug utilization worldwide and creating publications related to pharmacovigilance and drug safety.²⁰

After the thalidomide disaster, WHO set up the international drug monitoring programme with the goal of identifying rare adverse drug reactions that could not be found through clinical trial programs. Over time, the value of an international database of ADR case reports became more evident and the scope of the WHO programme has expanded. Today, the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, known as the Uppsala Monitoring Center (UMC), maintains the international database and serves the national pharmacovigilance centers that are associated with WHO and the monitoring programme.²¹ UMC's vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. In order to achieve its vision, UMC defines its mission as leading research and development of tools and methodologies for pharmacovigilance, leading and supporting global pharmacovigilance activities, developing effective networks for sustainable pharmacovigilance

systems, applying best practices for communication with stakeholders, providing high quality and cost-effective tools, services and dictionaries for pharmacovigilance terminologies, and building an effective organization for the future.²¹

There are currently 108 countries participating in the WHO programme, each with a national center that is appointed by the countries' governments. The national centers collect suspected ADR reports from health professionals. The case reports are then transferred to a WHO-specific format and submitted to UMC on a regular basis. Once received at the UMC, reports are checked for technical accuracy and then entered into the WHO database, called VigiBase. The Annual Report of activities covering the time period from June 2011 to July 2012 from UMC reported more than 7 million reports were present in VigiBase²². The WHO database is used to identify and review signals and is also considered an important reference source for national centers, pharmaceutical companies and other interested parties who have access to the largest and most comprehensive collection of adverse drug reactions. WHO has developed a set of programs to screen its database for potential signals, which are then communicated to the national centers. Signals can also be submitted to medical journals for publication. National centers have web-based applications that allow them free and complete access to the ADR reports entered in VigiBase.

While the value of collecting ADR reports from many countries into one single database cannot be denied, the present system is not without flaws. Olsson outlines several problems regarding the role of the WHO Programme on international drug monitoring in coordinating worldwide drug safety efforts. The first example Olsson describes is a delay in reporting due to the variation in frequency of reporting from national centers with some centers reporting every two weeks and others reporting only annually. VigiBase is also an incomplete database. Adverse

events are widely believed to be underreported, and many countries are without an adequate adverse drug reaction reporting system. Another example of a problem with VigiBase's signal detecting ability is the vast number of potential signals that can be derived as the tools used to analyze the data become more enhanced. With approximately 10,000 potential signals identified by WHO, the challenge lies in disregarding the "noise" in the data and selecting the few important true signals.¹⁷

In addition to identifying rare and serious adverse drug reactions, the UMC strives to disseminate important drug safety information from sources all around the world. WHO and the UMC have developed various tools to aid in the communication of global safety data including newsletters, reports, websites and email discussion groups. UMC has also developed training courses in adverse reaction reporting and monitoring for national centers' staff as well as healthcare professionals and has programs to assist in setting up new national centers. UMC is also in the unique position to gather information on processes and materials used in individual centers and then sharing that information so that unification and best practices can be developed.²²

WHO's efforts toward a global adverse reaction reporting database and resource have contributed to the larger effort towards harmonization of common pharmacovigilance standards and methodologies. Through its various programs, WHO has developed common definitions of pharmacovigilance terminology, organized meetings of international interested parties, maintained tools commonly used in drug safety such as WHOART and WHO Drug Dictionary and collaborated with other pharmacovigilance organizations such as the International Society of Pharmacoepidemiology (ISOE), the European Society for Pharmacovigilance (ESOP), the Drug Information Association (DIA) and CIOMS.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

ICH was formed in 1990. Unlike WHO, which holds a greater mission of worldwide public health, the specific goal of the ICH is to create and facilitate *harmonization* to ensure that safe, effective and high quality medicines are developed and registered. ICH brings together the drug regulatory agencies of Europe, Japan and the United States, along with the pharmaceutical industries from these three regions, to discuss scientific and technical aspects of product registration. ICH serves its mission through three major initiatives: 1. Tripartite guidelines; 2. MedDRA and; 3. The Common Technical Document (CTD). In March 1999, ICH created the Global Group (GCG) due to the growing interest of ICH initiatives in regions outside of the European Union, Japan and the U.S.. The GCG focuses its efforts on education and training in non-ICH countries interested in implementing ICH strategies, making ICH's efforts reach far-beyond its formative regions.

ICH guidelines are categorized into four areas – Quality, Safety, Efficacy and Multidisciplinary, which also represent the working groups that develop them. The Quality Guidelines have aided in the harmonization of the conduct of stability studies, standardization of impurity testing thresholds and the use of risk management in Good Manufacturing Practice. Efficacy Guidelines cover the design, conduct, safety and reporting of clinical trials. ICH Safety Guidelines have produced a comprehensive set of safety guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. As suggested by its name, the Multidisciplinary category covers topics that do not fit uniquely into one of the other main categories and includes guidelines on MedDRA, the CTD, which is the international standard for formatting and content requirements of marketing applications, and the Electronic Standards for

the Transfer of Regulatory Information (ESTRI).²³ As of July 2010, during ICH's 20th anniversary, approximately 75 guidelines had been finalized.²⁴

ICH topic E2E Pharmacovigilance Planning was finalized in November 2004 and was developed to aid in planning pharmacovigilance activities especially in preparation for the early postmarketing period of a new drug. In this Guidance, ICH describes the "Safety Specification" and "Pharmacovigilance Plan" as a part of the submission of a license application. The Safety Specification is defined as "a summary of the important identified risks of a drug, important potential risks, and important missing information."²⁵ The Safety Specification should also address the populations where the product is likely to be used and any outstanding safety questions that warrant further investigation to enhance understanding of the benefit-risk profile. The Safety Specification is then used to construct the Pharmacovigilance Plan. The Pharmacovigilance Plan is developed by the sponsor in conjunction with regulatory authorities during the application process. The ICH Guideline suggests that products that have no special safety concerns require only routine pharmacovigilance, which includes systems and provisions for adverse reaction reporting, expedited and periodic reporting of safety information and continuous monitoring of the safety profile. Products with important identified or potential risks or with important missing information require additional pharmacovigilance activities, which may include pharmacoepidemiological studies.²⁵ The E2E Guideline has been implemented in the European Union, Japan and the U.S. and is the basis of current understandings of risk management strategies, however the actual implementation differs among regions.

In addition to harmonization through guidelines, ICH developed MedDRA as a standardized medical terminology designed to facilitate sharing of regulatory information on

medicines internationally. MedDRA covers pharmaceuticals, vaccines and drug-device combination products and was implemented in 1999.

ICH also developed the Common Technical Document (CTD) as a common format for gathering the quality, safety and efficacy information that is required for product registration. The CTD has allowed for more efficient reviews of applications and has reduced duplication of efforts within industry. The CTD consists of five modules. Module 1 contains regional materials, while Modules 2-5 are intended to be common for all regions using the CTD format. In 2003, the CTD became mandatory for all new drug applications in the European Union and Japan, and is strongly recommended by the FDA in the U.S.. Marketing Authorisation Applications in Europe now require a Risk Management Plan as part of all submissions. The Risk Management Plan echoes the concepts of the Safety Specification and the Pharmacovigilance Plan as described in ICH's E2E Guideline and is located in Module 1 of the CTD in marketing applications.

The Council for International Organizations of Medical Sciences (CIOMS)

CIOMS is a non-governmental, international, non-profit organization that was established in 1949 through joint efforts of WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO). CIOMS defines its objectives as facilitating and promoting international activities in biomedical science, maintaining collaborative relations with the United Nations and its specialized agencies, and serving the scientific interests of the international biomedical community. To achieve these objectives, CIOMS coordinates four main programs: Bioethics, Health Policy, Ethics and Human Values, Drug Development and Use and International Nomenclature of Diseases. In 2012, CIOMS membership included 55 international, national and associate member organizations that encompass the biomedical industry, national academies of health science and medical research councils. A broad range of drug safety topics

has been covered by CIOMS via working groups. Working groups consist of scientists from regulatory authorities, pharmaceutical industry and academia who work together to develop consensus guidelines that are published and communicated internationally.²⁶

Under its Drug Development and Use Program, there are two subcategories of programs – Safety requirements for the use of drugs and Assessment and monitoring of adverse drug reactions and pharmacogenetics. There are also several working groups dedicated to pharmacogenetics, Standardised MedDRA Queries (SMQs), reporting and terminology of adverse drug reactions, vaccine pharmacovigilance, drug development research and pharmacovigilance in resource-poor countries.

In its final report, “Current Challenges in Pharmacovigilance: Pragmatic Approaches,” the CIOMS Working Group V writes, “the CIOMS Working Groups on drug safety have evolved an exciting dynamic vision: to enhance systems that advance public health, world-wide, through better assurance of the safety of medicinal products.” The first CIOMS Working Groups dedicated to drug safety issues were established in 1986. The initiatives created by these groups have been recognized for providing pragmatic platforms used to enhance the debate for harmonization of international pharmacovigilance practices. Many of the recommendations of the CIOMS Working Groups have been incorporated into regulations throughout the world. In addition to influencing regulation, several other international efforts, including ICH, have credited the work of the CIOMS Working Groups as the basis for the guidance they provide. The table below outlines major initiatives and achievements of various Working Groups in harmonized pharmacovigilance activities.²⁷

Table 2: Major Achievements of CIOMS Working Groups toward Harmonization in Pharmacovigilance²⁷

Working Group	Output	International Influence
I	<ul style="list-style-type: none"> Standardized definitions and criteria for ADR Reporting Creation of the CIOMS I Form for reporting serious ADRs 	Served as the model for the development of ICH Guideline E2A on expedited ADR case reporting for clinical trials
II	Standard format, content and frequency for periodic safety update reports (PSURs)	<ul style="list-style-type: none"> Adopted by many regulatory authorities Formed basis for ICH Guideline E2C on period reporting
III	Developed the concept of company core safety information (CCSI) and good safety information/labeling practices and the concept of Development Core Safety Information (DCSI) through Investigator's Brochures	<ul style="list-style-type: none"> Influenced the shape of requirements for the Summary of Product Characteristics in the EU Integral part of the ICH E2C Guideline
IV	Approaches for systemic handling of new safety signals as a tool for comparative benefit-risk assessment, options for action and good decision-making practices	

CIOMS V Working Group took over where previous Groups I - IV left off, attempting to address issues that were left unexplored or unresolved. CIOMS V focused on several aspects of day-to-day pharmacovigilance and published their proposals and recommendations in their final report in 2001. Its report proposes pragmatic approaches and principles in several key areas of pharmacovigilance including: sources of individual case reports, good case management practices, good summary-reporting practices, determination and use of population exposure data, and clinical safety reporting regulations.²⁷

The CIOMS V Working Group concluded its report acknowledging that much progress has been made in harmonization of pharmacovigilance practices and looked forward to the work that still needs to be done. The report reads, "Considerable progress has been made over the past

decade in achieving harmonization for many aspects of drug safety surveillance and reporting. However, much remains to be done in order to eliminate unnecessary differences and inefficiencies that command resources and time but add not real value to pharmacovigilance. The standards introduced under ICH and the proposals made by the various CIOMS Working Groups set an excellent precedent and should serve as a stimulus for better rationalization of international safety reporting requirements.”²⁷ In the twelve years since the CIOMS V Report, even greater progress has been made and many of the standards and recommendations made by CIOMS and ICH have, indeed, been integrated into the most current regulations and guidelines. Concepts, definitions, reporting requirements and formats increasingly approach harmonization internationally. More medicines are now available in more places in the world and more is known about the true safety and benefit of those medicines than ever before. This also means that new understandings of approaching pharmacovigilance globally and on a greater scale need to be developed even further for a truly harmonized system for ensuring safer medicines.

The Need for International Harmonization

The ICH, CIOMS and WHO initiatives have made great strides toward unification of global pharmacovigilance practices, however, a level of complete harmonization of adverse event reporting systems and risk management strategies does not yet exist. Definitions and reporting requirements still vary among regulatory authorities creating an environment where different data on the same product is submitted by manufacturers and healthcare practitioners to different authorities. When this happens, reactions to public health and safety can be varied or delayed.

The keys to successful pharmacovigilance in a modern world include enhanced global sharing of data, more effective communication of safety and efficacy of medicines to all parties

involved from manufacturers to healthcare professionals and patients, increased pharmacovigilance education in colleges and universities and a more dramatic shift away from reactive reporting of negative effects toward the proactive sharing of safety information on drugs and risk management.

Truly harmonized pharmacovigilance practices cannot be achieved until the areas of disharmony are identified and best practices are agreed-upon and implemented globally. While the idea of a harmonized system is widely discussed and studied, health authorities have failed to fully adopt policies and guidelines of global organizations such as ICH in their entirety. The tools are available for an environment where safety data of a medicine is shared and known in all areas where that medicine is available. International health authorities must use those tools in the same ways to allow for a truly global system. In the U.S. and E.U., pharmacovigilance regulations exist that define not only how the health authorities of these regions will address and manage the risks of medicinal products, but also how industry, healthcare professionals and consumers will be involved in those processes. These regulations are what shape the use of pharmacovigilance tools and are the key to unlocking where disharmony exists and how the national systems can be improved.

CHAPTER 3 – METHODOLOGY

Effective pharmacovigilance requires a system for collecting adverse drug reactions, methods for analyzing the data collected, systems for sharing safety data globally with effective communication tools and standards for reaction and policy regarding newly discovered safety information. Pharmacovigilance practices can be divided into adverse event reporting activities and risk management activities. This thesis examined pharmacovigilance legislation in the E.U. and U.S. in a comparative framework in order to establish the level of harmonization that exists in pharmacovigilance practices of these regions today. Because the legislation defines the practices of a particular region, comparing the regulations is an appropriate method for establishing where differences exist.

Methodical PubMed database searches were conducted to retrieve articles related to pharmacovigilance. Due to recent changes in the legislation of both regions and to guidelines published by international organizations, literature searches were limited to articles published in the last ten years to avoid inclusions of out-dated or no-longer-applicable results. Search terms included “pharmacovigilance,” “drug safety,” “pharmacovigilance harmonization,” “risk management” and “adverse event reporting.” Results included a number of study reports, scholarly reviews and expert opinion pieces and included diverse fields of study such as policy analysis, community behavior and public health research. The reference lists of each article were also reviewed in detail to find additional sources.

A review of the literature search results revealed a number of themes:

- Advances in pharmacovigilance practices have made safety information for medicines more readily available
- Harmonization of pharmacovigilance regulations and practices is required to ensure safer drug use
- The availability of medicines internationally means that more people are using more medicines than ever before
- Further advancements are needed, incorporating new technologies and methodologies, for protecting the public from the medicines that they take
- Divergent policies of regulatory bodies create unnecessary burdens for drug manufacturers and regulatory authorities and hinder the efforts toward protection of public health

These themes demonstrated that while substantial progress has been made in the field of pharmacovigilance, there remain still several voids to achieving a fully effective system. Harmonization has become a “buzz word” in the international pharmaceutical community where it has become clear that an increasingly global industry, so closely linked to public health, demands new and more comprehensive tools for pharmacovigilance. Through this framework, establishing the value of a harmonized system, the question of what level of harmonization exists today was raised.

The primary sources for establishing the current state of pharmacovigilance were the Food and Drug Administration (FDA) and European Medicines Agency (EMA) legislation related to drug safety reporting and risk management. Regulations were accessed via regulatory agency websites. Also critical were the published guidance documents of these regulatory bodies. The websites of the WHO, ICH and CIOMS organizations also served as valuable sources of

information, reports and guidelines describing current pharmacovigilance practices and recommendations. As global leaders in drug development and pharmacovigilance activities, the legislation and practices of the U.S. and E.U. were chosen as a reference point for establishing the current state of harmonization. While current views and guidelines stress the importance of a harmonized system, the question remains as to whether harmonization has been reached and to what extent.

In order to answer these questions and either establish a baseline pharmacovigilance system to implement globally or to identify where disharmonies exist and practices must evolve, the pharmacovigilance legislation in the U.S. was directly compared to that of the E.U.. Included in the comparison were any legislation related to adverse event reporting and risk management and the systems used to implement those legal requirements. A matrix was created to display the pharmacovigilance regulations and the systems in place to meet those requirements in both the U.S. and E.U.. Regulatory aspects were categorized into definitions, requirements and criteria for reporting and processes. The regulations were reviewed and the requirements in the U.S. were entered into the matrix. The E.U. regulations were then reviewed and entered into the matrix adjacent to the FDA equivalents. In cases where there was a regulatory requirement in the U.S. and no equivalent in the E.U., or vice versa, the definition, requirement or process was listed under its applicable region and “N/A” was entered in the column for the counterpart. The specific entries used for comparison were not predetermined, and the matrices’ were created in conjunction with the review of the legislation.

This display of the data allowed for analysis of where disharmony exists within the regulations. In order to assess the discrepant areas, each entry was not only compared between the two regions, but also with the practices described in the ICH guidelines. As an international

organization dedicated to global harmonization of practices involved in the development of medicines, ICH has become a standard for best practices and current thinking. An attempt at international harmonization of pharmacovigilance practices can begin with an alignment with ICH recommendations. By establishing where disharmony exists, recommendations for methods to harmonize the pharmacovigilance systems could be formed.

This thesis combined the information disbursed across the literature into a compressed and complete report of the state of pharmacovigilance in the E.U. and U.S.. The level of harmonization that currently exists was described through direct comparisons between the U.S. and E.U., and each region's legislation was compared to the recommendations and guidance of ICH.

CHAPTER 4 – RESULTS: DISHARMONY BETWEEN THE U.S. AND E.U.

Comparison of the Legislation

Current trends in pharmacovigilance include enhanced monitoring of the risk-benefit balance, a greater emphasis on post-marketing safety studies and a focus on prevention as opposed to reaction. Prevention means less focus on surveillance with the integration of risk management plans. It means shifting from generating alerts about new safety data to strengthened training of prescribing and use.

In addition to the authority granted to the FDA through the FD&C Act, the FDA's requirements for clinical and postmarketing safety reporting reside in the regulations. The table below outlines the sections of the law applicable to safety reporting.

Table 3: FDA Clinical and Postmarketing Safety Reporting Requirements for Drug Products

Regulation	Product Type
21 CFR § 312.32 ²⁸	Investigational new drugs
21 CFR § 314.80 ²⁹	Drugs with approved new drug applications
21 CFR § 314.98 ³⁰	Drugs with approved abbreviated new drug applications

A number of Drug Safety draft and final Guidances have been published by the FDA in recent years including Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Set (Final May 2013), Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft April 2013), Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format (Draft April 2013), Safety Reporting Requirements for INDs and BA/BE Studies (Final December 2013) among several others.³¹

Safety reporting legislation in the European Union is found in Directive 2001/20/EC³², Directive 2001/83/EC³³ and Regulation (EC) No 726/2004³⁴.

Table 4: Clinical and Postmarketing Safety Reporting Requirements for Drug Products

Regulation	Product Type
Directive 2001/20/EC ³²	Investigational new drugs
Directive 2001/83/EC ³³	Medicinal products for human use approved through the decentralized procedure
Regulation (EC) No 726/2004 ³⁴	Medicinal products for veterinary and human use approved through the centralized procedure

A key deliverable of the 2010 pharmacovigilance legislation was the Guideline on Good Pharmacovigilance Practices (GVP), which is a set of measures for effective pharmacovigilance in the E.U. divided into modules, each covering a major pharmacovigilance process.

Adverse Drug Reaction Reporting

Investigational Drug Safety Monitoring and Reporting

The safety reporting requirements for investigational drugs were found to be highly harmonized between the U.S. and E.U.. Three (3) out of four (4) definitions of terms that were compared were found to match (see Appendix 1, Table 1). The one term that was not considered an exact match was “Serious adverse event.” While both regions defined serious adverse events as any untoward medical occurrence that is fatal, life-threatening, results in or prolongs a hospitalization, results in a disability or incapacity, or is a congenital anomaly or birth defect, the U.S. definition allows for inclusion of significant medical events that may not qualify for one of the previously mentioned outcomes. This allowance for other “medically significant” events to be categorized as serious does not formally exist in the E.U. legislation. While the U.S. definition creates a more conservative approach to adverse event reporting requirements based on seriousness, the E.U. definition is directly aligned with the ICH definition as outlined in the E2A Guideline³⁵.

Table 5: Comparison of Legal Definitions of Investigational Drug Safety Terminology between the U.S. and E.U.

Term	E.U. matches U.S. Definition	E.U. matches ICH Definition	U.S. matches ICH Definition
Adverse event	Yes	Yes	Yes
Serious adverse event/Serious suspected adverse reaction	No	Yes	No
Suspected adverse reaction	Yes	Yes	Yes
Unexpected adverse event/Unexpected suspected adverse reaction	Yes	Yes	Yes

The U.S. and E.U. regulations were also harmonized in the specific reporting requirements that were compared. Both regions require Expedited 15-day reporting for serious, unexpected, suspected adverse reactions, and 7-day reporting for unexpected fatal or life-threatening suspected adverse reactions. Annual reports containing safety data are also required in both regions, though the content of the reports does differ. In the E.U., listings of suspected serious adverse reactions (i.e., only those events suspected to be related to the investigational product) are to be reported annually, while in the U.S., all serious adverse experience, regardless of relationship to study drug, are to be included in the Annual Reports (see Appendix 1, Table 2). The reporting format and inclusion as required in the U.S. matches the suggestions outlined by ICH in the E2F Guideline.³⁶

Table 6: Comparison of the Legal Requirements for Drug Safety Reporting on Investigational Products in the U.S. and E.U.

Requirement	E.U. matches U.S. Requirement	E.U. matches ICH Requirement	U.S. matches ICH Requirement
Expedited report, 15-day report	Yes	Yes	Yes
Expedited report, 7-day report	Yes	Yes	Yes

Annual Report	No	No	Yes
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Postmarketing Drug Safety Monitoring and Reporting

The recent advances and amendments to pharmacovigilance legislation in both the U.S. and E.U. have been concerned with safety reporting and monitoring in the postmarket environment. Both regions embarked on systematic reviews of their drug safety systems and determined that improvements were needed in postmarketing adverse event reaction reporting. The latest legislation does move toward harmonization of the drug safety systems of the U.S. and E.U., particularly when the goals of drug safety reporting, risk management and risk minimization are considered at a broader, more fundamental, level. When examined more closely, the details, specifics and mechanisms utilized by these regions to reach the goals of pharmacovigilance have not reached total harmonization. The way the regulations define terminology, the requirements for reporting or the processes and formats used to report all contain differences and disharmony.

The legal definitions of drug safety terminology, specific to adverse event reporting, which form the foundation of reporting requirements in the U.S. legislation did not align with European definitions. A major difference in the legislation in the U.S. focuses on “adverse drug experiences,” both related and unrelated, while the E.U. has shifted to requiring reporting only for “adverse reactions,” which by definition, are caused by the suspect medicinal product (see Appendix 2, Table 1). U.S. legislation contains definitions based on the concept of serious and unexpected adverse drug experiences, while the E.U. definitions are based on serious and unexpected adverse reactions (see Appendix 2, Table 1).

Table 7: Comparison of Legal Definitions of Post-Marketing Drug Safety Reporting Terminology between the U.S. and E.U.

Term	E.U. matches U.S. Definition	E.U. matches ICH Definition	U.S. matches ICH Definition
Adverse drug experience	N/A	N/A	Yes
Adverse reaction	N/A	Yes	N/A
Serious adverse drug experience	N/A	N/A	Yes
Serious adverse reaction	N/A	Yes	N/A
Unexpected adverse drug experience	N/A	N/A	Yes
Unexpected adverse reaction	N/A	Yes	N/A

Both regions have legislation in place that allows regulatory authorities to require an applicant to conduct postmarket studies. Both require applicants to have procedures in place for the surveillance, receipt, evaluation and reporting of adverse drug experiences. Several other areas showed partial harmonization or agreement, but differed in specific requirements. For example, expedited 15-day reports are required in both the U.S. and the E.U., however the reporting criteria for 15-day reports differs. In the U.S., applicants are to report all serious and unexpected adverse experiences, whether related or unrelated. In the E.U. Marketing Authorisation Holders (MAHs) are required to report all serious related adverse reactions, whether labeled or unlabeled (see Appendix 2, Table 2). In this case, the U.S. regulation is in-line with the ICH guidance found in the E2D Guideline on Post-approval Safety Data Management.³⁷

In addition to the 15-day expedited report required in both the U.S. and the E.U., the E.U. has an additional requirement for 90-day reports on all non-serious suspected adverse reactions – a provision that does not exist in U.S. legislation. In the U.S., non-serious events, whether suspected or not, are reported only periodically, as is recommended in the ICH E2D Guideline³⁷ (see Appendix 2, Table 2).

Both regions have a designated form for expedited reporting, but they are unique (FDA Form 3500A in the U.S. and CIOMS I Form in the E.U.). Reporting, both expedited and periodic, is conducted in the E.U. electronically to designated databases. In the U.S., expedited and periodic reports are sent in duplicate copy to the Central Document Room (see Appendix 2, Table 3).

Another example of disharmony between the U.S. and E.U. in post-approval safety reporting is non-expediting periodic reporting. Periodic Safety Update Reports (PSUR) are required in both the U.S. for reporting of adverse experiences that are not reported in 15 or 90-day reports. In the U.S., PSURs are required on a quarterly basis for the first three years after approval and then annually. As of April 2013, PSURs in the E.U. are to be reported on a harmonized schedule according to the E.U. Reference Date List for medicines. This harmonized reporting schedule for all products of the same active substance is directly aligned with the concepts outlined in ICH’s E2C(R2) Guideline³⁸ (see Appendix 2, Table 2). In addition, the E.U. requirements for the content of period reports are more in-line with the scientific evaluation of the risk-benefit balance (see Appendix 2, Table 3) as in ICH Guideline E2C(R2).³⁸

Table 8: Comparison of Postmarketing Drug Safety Reporting Requirements and Responsibilities in the U.S. and E.U.

Requirement	E.U. matches U.S. Requirement	E.U. matches ICH Requirement	U.S. matches ICH Requirement
Postmarket studies and clinical trials	Yes	Yes	Yes
Development of procedures	Yes	Yes	Yes
Expedited 15-day reports	No	No	Yes
Expedited 90-day reports	N/A	No	Yes
Periodic adverse drug experience reports	No	Yes	No

Risk Management

The FDA defines risk management as “an iterative process of (1) assessing a product’s benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluation tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance.”¹⁸ The definition of risk management in the E.U. is very similar – “a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product including the assessment of the effectiveness of those activities and interventions.”¹⁹ In the U.S., risk management is achieved through Risk Evaluation and Mitigation Strategies (REMS) and Risk Minimization Action Plans (RiskMAPs), while in the E.U., Risk Management Plans (RMPs) and Pharmacovigilance Systems are utilized (see Appendix 2, Table 1). Provisions are in place in both regions for systematic risk management and minimization, though the specific aspects of risk management addressed in each region differ. Terminology exists in the E.U. legislation that does not exist in the U.S. including, “pharmacovigilance system” and “pharmacovigilance system master file.”

Table 9: Comparison of Legal Definitions of Risk Management Terminology between the U.S. and E.U.

Term	E.U. matches U.S. Definition	E.U. matches ICH Definition	U.S. matches ICH Definition
Risk management system	No	Yes	No
Risk management plan	N/A	Yes	N/A
Risk minimization action plan (RiskMAP)	N/A	N/A	Yes
Pharmacovigilance system	N/A	Yes	N/A

Pharmacovigilance system master file	N/A	Yes	N/A
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European legislation has formalized post-marketing pharmacovigilance requirements through the Pharmacovigilance System and Pharmacovigilance System Master File. The Pharmacovigilance System requires a MAH to:

- have access to a Qualified Person responsible for Pharmacovigilance (QPPV)
- maintain a Pharmacovigilance System Master File (PSMF) that is available for inspection upon request
- operate a risk management system for each medicinal product
- monitor the outcome of risk minimization measures in the RMP
- update and monitor the risk management system

The PSMF has become a major component to the pharmacovigilance-related information in marketing applications in the E.U. (see Appendix 2, Table 2). This document, which must be available for audit upon request, describes in great detail the entire pharmacovigilance system in place for a medicinal product, including the processes used to monitor the safety profile, manage the known risks and react to newly discovered information.

While the concept behind REMs and RMSs may be comparable, the ways that those concepts are applied differ so greatly, that the terms cannot be considered as harmonized counterparts. In the E.U. details of the MAH's pharmacovigilance system must be included in all marketing applications, and risk management plans are a required part of the pharmacovigilance system. The specific requirements for MAHs include the scientific evaluation of all safety information and strategies for minimizing and preventing unnecessary risk. A risk management plan must contain the same basic sections for each medicinal product, which include: product

overview, safety specification, pharmacovigilance plan, plans for post-authorization studies, risk minimization measures, summary information, and specific annexes. GVP Module V states that “ICH-E2E defines two basic parts of a RMP: the safety specification and that pharmacovigilance plan. It does not include risk minimisation. However it was acknowledged at the time of development of ICH-E2E that risk minimisation was an integral part of risk management planning.”¹⁹ Unlike in the E.U., REMS are required only for products which the FDA deems hold an exceptional level of risk which requires additional risk management. REMS are also less focused on the systematic evaluation of risks and how best to manage those risks, and are generally made up of a Medication Guide and/or a Communication Plan for healthcare professionals. A RiskMAP is a strategy used, when required by the FDA, to outline specific goals for assessing strategies used in minimizing risks while maintaining benefits see Appendix 2, Table 1, Table 2 and Table 3).

Other Components of Pharmacovigilance

Other than adverse event reporting and risk management, the pharmacovigilance legislation in both the U.S. and E.U. contain requirements for Quality, including written procedures and record-keeping. Both regions do require written procedures to be in place for all activities related to pharmacovigilance. In the E.U., the procedures are part of the Pharmacovigilance System Master File. While both sets of regulations do contain requirements for recordkeeping, the mandatory time for manufacturers to retain records differs. In the U.S., records on all adverse drug experiences must be maintained for 10 years. The E.U. requires maintaining records for as long as the product is authorized and for at least 10 years after the product is no longer marketed (see Appendix 2, Table 2).

Another area of disharmony between the U.S. and E.U. is in the technical formatting and submission processes for safety data submissions. While the FDA still relies heavily on a paper-based submission system, requiring manufacturers to submit paper copies of MedWatch forms and periodic reports, the E.U. is now requiring all applicants to submit 15-Day Alerts as well as periodic reports electronically through EudraVigilance. In addition, the FDA still requires the use of its own MedWatch Form 3500A for reporting individual adverse events, while in the E.U., the CIOMS standardized form is required.

A State of Disharmony

When examining the trends of pharmacovigilance activities shifting from reactive to proactive approaches alongside the common discussion and enhanced value placed on management of risks that are associated with the use of medicines, it would appear that the basic understanding of the role of pharmacovigilance is harmonized in the U.S. and the E.U.. However, when specific components of pharmacovigilance are directly compared, it is revealed that the ways in which that universal understanding of the role of pharmacovigilance is implemented are not harmonized. While the need to revise and expand pharmacovigilance regulations was recognized in both regions in recent years, the results contain disparity and disagreement.

Concerning adverse event reporting, major discrepancies exist between the specific data that is collected by international regulatory agencies. Different types of data are collected in different formats and on different frequencies. Risk management is conducted in completely divergent modes, with specific aspects of ICH recommendations found integrated in various sections of the legislation in both regions, though the same aspects are not always integrated in both regions, nor are they always integrated in the same ways.

CHAPTER 5 – CONCLUSIONS: THE FUTURE OF PHARMACOVIGILANCE

Adverse event reporting remains a major component of pharmacovigilance. While the tools and methods for adverse event reporting have certainly progressed, international agreement regarding what should be reported and how has not been reached. Since creating the VigiBase reporting system, WHO has endorsed the value of and encouraged the use of a comprehensive, worldwide database for adverse event data. However, since the responsibility for reporting to this database lies in the hands of national centers, who receive their data based on the local regulations and practices in their individual countries, a lack of harmonization at a national level, creates a disparity and inconsistency within the one system that intends to be a global resource. Reports received from one country cannot necessarily be directly compared to or grouped with those received from another as varying legal requirements create two separate and different sets of data. For example, in line with ICH guidance, FDA requires manufacturers to report serious, unexpected, related and not related events as expedited 15-day alerts. FDA seems to believe that even those events that healthcare professionals and consumers may not see as being possibly related to a medicine can reveal potential signals that can lead to completely new understandings of the effects of drugs. In the E.U., on the other hand, only those events that are considered to be related to the medicinal product by the reporter are required to be submitted as 15-day alerts. This means that data collection and submission to WHO in the E.U. is much more limited in scope than that from the U.S., again, creating a set of data that is potentially disproportionate and incomparable.

While reporting rates for adverse drug reactions have increased over the years, studies have shown a high rate of underreporting in both daily practice and clinical trial. Less than 10% of serious adverse drug reactions and only 2-4% of non-serious adverse reactions are reported to health authorities.³⁹ In addition, the relatively small number of reactions that are reported, come disproportionately from the developed versus the developing world. In 2000, the WHO database was updated with 549,100 reports. The top 11 reporting countries were the U.S., U.K., France, Australia, Spain, Germany, New Zealand, Canada, the Netherlands and Sweden. Only 14,463 reports were received from all other countries, which includes the developing world and which accounts for over 80% of the world population.³⁷ This discrepancy means that spontaneous reporting is far less useful for adverse reactions that are unique to the developing world or when an adverse reaction is a result of a particular use of a medicine within a given community.

In *The Importance of Pharmacovigilance*¹, published by WHO, the need for the review and further development of pharmacovigilance systems in light of various challenges is discussed. Among their recommendations, WHO states that its priorities for improving the detection of adverse drug reactions include: improving identification of ADRs by healthcare providers and patients, greater use of epidemiological methods to monitor drug safety concerns, enhancing expertise for concerns specifically related to vaccines, biologics veterinary medicine, herbal medicines, biotechnology products and investigational drugs, making ADR data with international relevance available more rapidly, revisiting definitions or terms related to pharmacovigilance and developing systems that benefit populations with limited access to health care.¹

Like adverse drug reaction reporting, current risk management strategies are not without issues and challenges. Risk management is a concept that has been examined extensively in

recent years by both regulatory authorities and international organizations, like ICH. The most recent guidelines and best practices have formalized the processes for establishing the safety profile of a medicine as well as implementing strategies to minimize those risks. Major concepts have also stressed the importance of a harmonized evaluation of drug safety – both within products with the same active ingredients as well as among the international pharmacovigilance environment. The most recent risk management legislation in the EU moves pharmacovigilance practices toward this new direction, however until the U.S. and other health authorities also implement these concepts in their risk management strategies, a truly harmonized system will not be reached. Current risk management legislation in the U.S. and EU are completely disharmonized. Differences exist in both the requirements and use of risk management strategies and the threshold for taking action once a safety issue is discovered. Even the basic concepts of what risk management is and how it is best implemented are not aligned.

This means that when drugs are withdrawn from the market for safety reasons, there is often a disparity in the regulatory decisions in the U.S. and EU. The main concern in disharmonized risk management strategies are the inconsistencies in interpretation of safety information. Hirst *et al.* outline 22 drug withdrawals in the U.S. and EU between 1997 and 2005. In 10 of those cases, there was a disparity in regulatory decisions between the U.S. and EU, demonstrating the disagreement on major risk management decisions across international borders.⁴⁰ This weakness in international risk management suggests that a more harmonized system is needed.

In addition to decision-making inconsistencies, there are many countries in the world that have limited resources for funding risk management efforts. Again, a harmonized international system would aid those countries and allow for better drug safety. Part of risk management is the

development and utilization of specific tools to minimize risks. This in itself is a challenge for pharmacovigilance professionals who must work a fine line between the communication of and education about risks, providing tools to minimizing risks, and not impose hurdles to prescribing physicians.⁴⁰

Recommendations for the Future of Pharmacovigilance

While much progress has been made in pharmacovigilance practices, many of the deficiencies and issues that still exist in efforts for safer medicines and medicine usage, could be resolved with a harmonized international system. Harmonization goes beyond regulation. It requires “best practices” for healthcare professionals as well as industry and regulatory authorities. It requires formalized training for pharmacovigilance professionals and better communication tools. Safety information is communicated between regulatory agencies, regulatory agencies and manufacturers, healthcare professionals and manufacturers, agencies and healthcare professionals, healthcare professionals and consumers. All of those parties in communication utilize different tools – from product labeling to adverse event reports. In today’s technological environment these communications are occurring more frequently over the Internet, through social media and the Cloud. For pharmacovigilance practices to remain current on an international level, pharmacovigilance practices must embrace and take advantage of these modes of communication.

Studies have explored the use of technology in pharmacovigilance. In Cambodia, a pilot study of text-message based adverse event reporting system was tested from a single vaccination center.⁴¹ The amount of safety data on medicines available to regulatory agencies, industry, healthcare professionals and consumers will continue to grow. Moore wrote that “Social media will certainly play a major role in the early identification of alerts. It is possible that Google

trends will be the future alerting system...How individual medical files will be incorporated into the Cloud and made available remains uncertain. One certainty is that as computing grows even more powerful, the capacity to identify minute differences may overtake the capacity to identify or include biases, resulting in the distinct risk of being overwhelmed by statistically “significant” differences that are clinically irrelevant. This might have the good effect of placing more importance on common sense and medical judgment.”⁴² The modes for collecting adverse event data are directly correlated to the need for harmonized pharmacovigilance practices. Use of the internet means that data not only *can be* shared instantaneously worldwide, but that it *will be* shared. Pharmacovigilance professionals must use these trends to their advantage and the enhancement of public health.

While this thesis identified that specific areas of disharmony that exist in the Pharmacovigilance legislation of the U.S. and E.U. today, it is just a glimpse into a small segment of the international pharmacovigilance environment. While these two regions represent major players in global development of medicines and are major sources of safety information, they do not represent the majority of the population of the world utilizing those medicines. Harmonization must include all stakeholders to be truly effective in aiding in the efforts towards safer use of medicines and greater public health. Addressing discrepancies between two regions with well-established pharmacovigilance systems is a starting point for establishing completely new systems where none exist today. While the reach of pharmacovigilance must be considered globally, the efforts to harmonize must begin with the most influential and involved organizations that exist today.

Identifying the discrepancies in existing practices is also only a first step. More work is required to establish the best practices, tools and infrastructure that will be required to address

the needs of pharmacovigilance in the future. International organizations must continue to advance their understanding of pharmacovigilance and establish guidelines for shifting away from a focus on finding harm and more toward extending knowledge about safety to all appropriate stakeholders. Wallace and Evans write, “Pharmacovigilance should operate in a culture of scientific development. This requires the right balance of inputs from various disciplines, a stronger academic base, greater availability of basic training, and resource which is dedicated to scientific strategy.”⁴³ Of course, implementing such strategies will require legislative change; thus the process that begins with the legislation to identify where disharmony exists, must also end with the legislation to create a framework at a national level that allows for an international harmonization of practice.

Future study is needed to accurately characterize the true state of harmonization in pharmacovigilance practices. Comparisons must go beyond the environments of the U.S. and E.U. and must involve a more global view. In addition, comparing legislation may not necessarily reveal the actual practices of a region; study of reporting and risk management trends must also be conducted. An interesting component of assessing the state of pharmacovigilance would also be to consider the views and perspectives of various stakeholders in drug safety. Regulatory authorities have insight on the value of the legal requirements in the regions. Pharmacovigilance professionals have insight on the burden of those requirements and the existing disharmony. Healthcare professionals and consumers can reveal the level of awareness of pharmacovigilance requirements and the day-to-day practices. Harmonization of pharmacovigilance is needed, and this type of work and study will be required in order to progress and change to occur.

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APPENDICES

Appendix 1 – Investigational Product Pharmacovigilance Legislation

Table 1: Comparison of Legal Definitions of Investigational Drug Safety Terminology between the U.S. and E.U.

	United States	European Union
Adverse event	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR §312.32(a))	Any untoward medical occurrence in a patient of clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment (Directive 2001/20/EC, Article 2 (m))
Serious adverse event or Serious suspected adverse reaction	An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (21 CFR §312.32(a))	“serious adverse event or serious adverse reaction” any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in a persistent or significant disability or incapacity, or is a congenital anomaly or birth defect (Directive 2001/20/EC, Article 2 (o))
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. “Reasonable possibility” means there is evidence to support a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. (21 CFR §312.32(a))	“adverse reaction” All untoward and unintended responses to an investigational medicinal product related to any dose administered (Directive 2001/20/EC, Article 2 (n))
Unexpected adverse event or Unexpected suspected adverse reaction	An adverse event of suspected adverse reaction that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general	“unexpected adverse reaction” An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator’s brochure for an unauthorized investigational product or summary of product characteristics for an authorized product) (Directive 2001/20/EC, Article 2 (p))

	investigational plan or elsewhere in the current application, as amended. (21 CFR §312.32(a))	
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Table 2: Comparison of the Legal Requirements for Clinical Drug Safety Reporting in the U.S. and E.U.

	United States	European Union
Expedited report, 15-day report	<p>Must be reported to FDA and all investigators:</p> <ul style="list-style-type: none"> • Serious and unexpected suspected adverse reactions • Findings from other studies (epidemiological studies, pooled analysis of studies, or other IND or non-IND studies) that suggest a significant risk to humans exposed to the drug • Findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure • Increased rate of occurrence of serious suspected adverse reactions (21 CFR §312.32(c)(1)) 	<p>All other [not fatal or life-threatening] suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor (Directive 2001/20/EC, Article 17, 1 (b))</p> <p>Sponsor shall also inform all investigators (Directive 2001/20/EC, Article 17, 1(d))</p>
Expedited report, 7-day report	<p>Report to FDA any unexpected fatal or life-threatening suspected adverse reaction (21 CFR §312.32(c)(2))</p>	<p>The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days. (Directive 2001/20/EC, Article 17, 1(a))</p> <p>Sponsor shall also inform all investigators (Directive 2001/20/EC, Article 17, 1(d))</p>
Annual Report	<p>A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigations that includes</p>	<p>Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which</p>

	<ul style="list-style-type: none"> • Individual study information to include study titles, number of subjects, final or interim results • Summary information including narrative or tabular summary of most frequent and most serious adverse experiences by body system, summary of all IND safety reports submitted in the past year, list of subjects who died during participation in the study, list of subjects who dropped out of the study due to adverse experience, a brief description of what has been learned regarding the drug's action, list of preclinical studies, a summary of any significant manufacturing or microbiological changes • Description of the general investigational plan • Description of any relevant changes to the Investigator Brochure • Description of significant Phase 1 protocol modifications • Brief summary of significant foreign marketing developments • A log of outstanding business (21 CFR §312.33) 	<p>have occurred over the period and a report of the subjects' safety (Directive 2001/20/EC, Article 17, 2)</p>
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Table 3: Comparison of Technical Requirements for Reporting of Clinical Drug Safety Data in the U.S. and the E.U.

	United States	European Union
Format for reporting adverse drug reactions	Accepted formats to submission to FDA: <ul style="list-style-type: none"> • Narrative format • FDA Form 3500A • An electronic format that can be processed, reviewed and archived by FDA (in accordance with current FDA guidance for electronic format) • CIOMS I form if foreign suspected adverse reaction(21 CFR §312.32(c)(1)(v)) 	N/A

Appendix 2 - Marketed Product Pharmacovigilance Legislation

Table 1: Comparison of Legal Definitions of Postmarketing Pharmacovigilance Terminology in the U.S. and E.U.

	United States	European Union
Adverse drug experience	Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action (21 CFR §314.80(a))	N/A
Adverse reaction	N/A	A response to a medicinal product which is noxious and unintended (Directive 2001/83/EC, Title I, Article 1, 11)
Serious adverse drug experience	Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (21 CFR §314.80(a))	N/A
Serious adverse reaction	N/A	An adverse reaction which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect (Directive 2001/83/EC, Title I, Article 1, 12)
Unexpected adverse drug experience	Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from	N/A

	the event because of greater severity or specificity. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product. (21 CFR §314.80(a))	
Unexpected adverse reaction	N/A	An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics (Directive 2001/83/EC, Title I, Article 1, 13)
Risk management system	An iterative process of (1) assessing a product’s benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance (FDA RiskMAP Guidance)	A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions (Directive 2001/83/EC, Title I, Article 1, 28b)
Risk management plan	N/A	A detailed description of the risk management system (Directive 2001/83/EC, Title I, Article 1, 28c)
Risk Minimization Action Plan (RiskMAP)	A strategic safety program designed to meet specific <i>goals</i> and <i>objectives</i> in minimizing known risks of a product while preserving its benefits (FDA RiskMAP Guidance)	
Pharmacovigilance system	N/A	A system used by the marketing authorization holder and by Member States to fulfill the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance (Directive 2001/83/EC, Title I, Article 1, 28d)
Pharmacovigilance system master file	N/A	A detailed description of the pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized medicinal products (Directive 2001/83/EC, Title I, Article 1, 28e)

Table 2: Comparison of Postmarketing Pharmacovigilance Requirements and Responsibilities in the U.S. and E.U.

	United States	European Union
Review of adverse drug experiences	Applicants must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. (21 CFR §314.80(b))	N/A
Postmarket Studies and Clinical Trials	Applicants may be required to conduct post-approval study or studies of the drug, or a postapproval clinical trial or trials of the drug if the Secretary deems it necessary for the following: <ul style="list-style-type: none"> • To assess a known serious risk related to the use of the drug involved • To assess signals of serious risk related to the use of the drug • To identify an unexpected serious risk when available data indicates the potential for serious risk (21 U.S.C. § 355(o)(3)) 	After the granting of a marketing authorization, the national competent authority may impose an obligation on the marketing authorization holder: (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorized medicinal product. If the same concerns apply to more than once medicinal product, the national competent authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorization holders concerned to conduct a joint post-authorisation safety study (Directive 2001/83/EC, Title IX, Chapter 1, Article 22a)
Risk evaluation and mitigation strategies	If deemed necessary, a REMS must be submitted with marketing application (21 U.S.C. § 355-1(a))	The marketing authorization holder shall by means of the pharmacovigilance system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimization and prevention and take appropriate measures as necessary (Directive 2010/84/EU, Title IX, Chapter 1, Article 104 (2)) As part of the pharmacovigilance system, the marketing authorization holder shall:... (c) operate a risk management system for each medicinal product (Directive 2010/84/EU, Title IX, Chapter 1, Article 104 (3) (c))
Pharmacovigilance System	N/A	Applicants shall operate a pharmacovigilance system for fulfillment of their pharmacovigilance tasks which will be used to collect information on the risks of medicinal products as regards patients' and public health. (Directive 2001/83/EC, Title IX, Chapter 1, Article 101, 1)

		<p>MAH must use the Pharmacovigilance System to evaluate all information scientifically, consider options for risk minimization and prevention and take appropriate measures as necessary (Directive 2001/83/EC, Title IX, Chapter 1, Article 101, 2)</p> <p>Requirements of the PV system:</p> <ul style="list-style-type: none"> the MAH shall have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance who resides and operates in the EU and is responsible for the establishment and maintenance of the PV system maintain and make available on request a pharmacovigilance system master file operate a risk management system for each medicinal product monitor the outcome of risk minimization measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorization update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products <p>(Directive 2001/83/EC, Title IX, Chapter 1, Article 104, 3)</p>
Development of Procedures	Applicants shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experience to FDA. (21 CFR §314.80(b))	MAHs shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. Submitted electronically to Eurdravigilance (Directive 2001/83/EC, Title IX, Chapter 3, Article 107, 4)
Expedited 15-day Reports	The applicant shall report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant (21 CFR §314.80(c)(1)(i))	<ul style="list-style-type: none"> MAHs shall submit electronically to Eurdravigilance information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the MAH concerned

		<p>gained knowledge of the event (Directive 2001/83/EC, Title IX, Chapter 3, Article 107, 3)</p> <ul style="list-style-type: none"> Member States shall, within 15 days following receipt of the reports of serious suspected adverse reactions from healthcare professionals and patients, submit the reports electronically to the Eudravigilance database (Directive 2001/83/EC, Title IX, Chapter 3, Article 107a, 4)
Expedited 90-Day reports	N/A	<ul style="list-style-type: none"> MAHs shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the MAH concerned gained knowledge of the event (Directive 2001/83/EC, Title IX, Chapter 3, Article 107, 3) Member States shall within 90 days following receipt of the reports of non-serious suspected adverse reactions from healthcare professionals and patients, submit the reports electronically to Eudravigilance (Directive 2001/83/EC, Title IX, Chapter 3, Article 107a, 4)
Periodic adverse drug experience reports	The applicant shall report each adverse drug experience not reported under a 15-Day alert report at quarterly intervals, for 3 years from the date of approval of this application, and then at annual intervals. The applicant shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. (21 CFR §314.80(c)(2))	The list of EU reference dates and frequency of submission of PSURs consists of a comprehensive list of substances and combinations of active substances in alphabetical order, for which PSURs, where required, shall be submitted in accordance with the EU reference date and the frequency as determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) following consultation with the Pharmacovigilance and Risk Assessment Committee (PRAC). (GVP Module VII)
Recordkeeping	Applicant shall maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relation to adverse drug experiences. (21 CFR §314.80(i))	Pharmacovigilance data and documents relating to individual authorized medicinal products shall be retained as long as the product is authorized and for at least 10 years after the marketing authorization has ceased to exist. However, the documents shall be retained

		for a longer period where Union law or national law so requires [IR Art 12 (2)]. (GVP Module 6 p. 24)
Enforcement	If applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application. (21 CFR §314.80(j))	<p>Safety concerns can be identified by Member states as a result of the evaluation of data resulting from pharmacovigilance activities, and urgent safety procedures in concerned Member States are initiated if a Member State notifies the Union of any the following:</p> <ul style="list-style-type: none"> • it considers suspending or revoking a marketing authorization; • it considers prohibiting the supply of a medicinal product; • it considers refusing the renewal of a marketing authorization • it is informed by the MAH that, on the basis of safety concerns, he has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorization withdrawn, or that he intends to do so; • it considers that new contraindication, a reduction in the recommended dose, or a restriction to the indications is necessary(Directive 2001/83/EC, Title IX, Chapter 3, Article 107i, 1) <p>Urgent safety procedures result in a recommendation from the Pharmacovigilance Risk Assessment Committee within 60 days. Recommendations shall include any or a combination of the following conclusions:</p> <ul style="list-style-type: none"> • no further evaluation or action is required at Union level; • the MAH should conduct further evaluation of data together with the follow-up of the results of that evaluation; • the MAH should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study; • the Member States or MAH should implement risk minimization measures; • the marketing authorization should be suspended, revoked or not renewed;

		<ul style="list-style-type: none"> the marketing authorization should be varied(Directive 2001/83/EC, Title IX, Chapter 3, Article 107j, 3)
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Table 3: Comparison of Technical Postmarketing Reporting Requirements in the U.S. and E.U.

	United States	European Union
How to submit 15-day Report	Applicant shall report to FDA adverse drug experience information, as described in this section. The applicant shall submit two copies of each report described in this section to the Central Document Room... (21 CFR §314.80(c))	Submitted electronically to Eurdravigilance (Directive 2001/83/EC, Title IX, Chapter 3, Article 107, 3)
How to submit 90-Day Report	N/A	Submitted electronically to Eurdravigilance (Directive 2001/83/EC, Title IX, Chapter 3, Article 107, 3)
How to submit Periodic Reports	Applicant shall report to FDA adverse drug experience information, as described in this section. The applicant shall submit two copies of each report described in this section to the Central Document Room...(21 CFR §314.80(c))	Submitted electronically (Directive 2001/83/EC, Title IX, Chapter 3, Article 107b, 1)
Content of periodic report	<ul style="list-style-type: none"> A narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval A FDA form 3500A (Adverse Reaction Report) for each adverse drug experience not reported in a 15-day Alert History of action taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated) (21 CFR §314.80(c)(2)(ii)) 	<ul style="list-style-type: none"> Summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorization Scientific evaluation of the risk-benefit balance of the medicinal product All data relating to the volume of sales of the medicinal product and any data in possession of the MAH relating to the volume of prescription, including an estimate of the population exposed to the medicinal product (Directive 2001/83/EC, Title IX, Chapter 3, Article 107b, 1)
Inclusion in periodic report	Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse drug experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the	The evaluation of risk-benefit shall be based on all available data, including data from clinical trials in unauthorized indications and populations (Directive 2001/83/EC, Title IX, Chapter 3, Article 107b, 1)

	scientific literature, and from marketing experience (21 CFR §314.80(c)(2)(iii))	
Content of proposed Risk evaluation and mitigation strategies	The Secretary may require that the REMS include 1 or more of the additional elements: <ul style="list-style-type: none"> • Medication guide and patient package insert • Communication plan for healthcare professionals (21 U.S.C. § 355-1(e)) 	N/A
Content of risk management plan	N/A	7 parts: <ol style="list-style-type: none"> 1. Product overview 2. Safety specification 3. Pharmacovigilance plan 4. Plans for post-authorisation efficacy studies 5. Risk minimization measures (including evaluation of the effectiveness of risk minimization measures) 6. Summary of the risk management plan 7. Annexes (GVP Module V)
Form for U.S. reports	FDA Form 3500A (21 CFR §314.80(f))	Electronic reporting is mandatory [DIR Art 107(3), Art 107a(4)]
Form for foreign reports	FDA Form 3500A or CIOMS I (21 CFR §314.80(f))	Electronic reporting is mandatory [DIR Art 107(3), Art 107a(4)]