Comparison of EU-Pharmacovigilance System Master File (PSMF) with US System

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To my family for their patience and their assistance

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List of Abbreviations

ANDA	**A**bbreviated **N**ew **D**rug **A**pplication
BLA	**B**iologic **L**icense **A**pplication
CBER	**C**enter for **B**iologics **E**valuation and **R**esearch
CDER	**C**enter for **D**rug **E**valuation and **R**esearch
CFR	**C**ode of **F**ederal **R**egulations
CIOMS	**C**ouncil for **I**nternational **O**rganization of **M**edical **S**cience
CTD	**C**ommon **T**echnical **D**ocument
DCP	**D**e**c**entralized **P**rocedure
DDPS	**D**etailed **D**escription **P**harmacovigilance **S**ystem
EEA	**E**uropean **E**conomic **A**rea
EMA	**E**uropean **M**edicine **A**gency
EU	**E**uropean **U**nion
FAERS	**F**DA's **A**dverse **E**vent **R**eporting **S**ystem
FDA	**F**ood and **D**rug **A**dministration
FDAAA	**F**ood and **D**rug **A**dministration **A**mendments **A**ct
FDCA	**F**ood, **D**rug and **C**osmetic **Act**
GVP	**G**ood **V**igilance **P**ractice
HCT/P	**H**uman **C**ellular and **T**issue based **P**roduct
ICH	**I**nternational **C**onference on **H**armonization
ICSR	**I**ndividual **C**ase **S**afety **R**eport
IND	**I**nvestigational **N**ew **D**rug

IOM	**I**nstitute **O**f **M**edicine
IR	Commission **I**mplementing **R**egulation (EU) No 520/2012
MAH	**M**arketing **A**uthorization **H**older
MedWatch	**Med**ical Product Reporting Program
MRP	**M**utual **R**ecognition **P**rocedure
NDA	**N**ew **D**rug **A**pplication
OTC	**O**ver **T**he **C**ounter
PDUFA III	**P**rescription **D**rug **U**ser **F**ee **A**ct **III**
PHS Act	**P**ublic **H**ealth **S**ervice **Act**
PSMF	**P**harmacovigilance **S**ystem **M**aster **F**ile
PSUR	**P**eriodic **S**afety **U**pdate **R**eport
PV	**P**harmaco**v**igilance
QPPV	**Q**ualified **P**erson for **P**harmaco**v**igilance
REMS	**R**isk **E**valuation and **M**itigation **S**ystem
RiskMAP	**Risk M**inimization **A**ction **P**lan
RMS	**R**isk **M**anagement **S**ystem
THMP	**T**raditional **H**erbal **M**edicinal **P**roduct
USC	**U**nited **S**tates **C**ode
VAERS	**V**accine **A**dverse **E**vent **R**eporting **S**ystem
WHO	**W**orld **H**ealth **O**rganization
XEVMPD	E**x**tended **E**udra**v**igilance **M**edicinal **P**roduct **D**ictionary
XEVPRM	E**x**tentend **E**udra**v**igilance Medicinal **P**roduct **R**eport **M**essage

Introduction

The decision of approving a medicinal product is based on its satisfactory balance between benefits and risks within the conditions specified in the product's labeling. This decision is also based on the limited information available at the time of approval. The knowledge related to the safety profile of the medicinal products can change over time through expanded use, specifically in terms of patient characteristics and the number of exposed population. In the post-marketing period, the medicinal product might be used in settings completely different from the clinical trials before approval of the marketing authorization application - in other words, a much larger population with a diverse range of co-morbid conditions or treated with several concomitant medicinal products might be exposed in a relatively short timeframe.[1]

The huge exposure to the medicinal product in the post-marketing period will generate new information, which can have an impact on benefits or risks of the medicinal product. Detailed documenting of the mentioned information and continuation of evaluations are important for all products to ensure their safe and effective use. Furthermore, the benefit-risk balance can be improved by reducing risks through applying special conditions and limitations for using the medicinal product and by delivering information to the prescribing physicians or to the users of medicinal products in a timely manner.

According to the definition of the World Health Organization (WHO), Pharmacovigilance (PV) is "the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug related problems". The mentioned definition encompasses the knowledge and the all activities needed for the safe and effective use of the medicinal products.[2]

The etymological roots for the word "Pharmacovigilance" are: "Pharmakon" (Greek for drug) and "Vigilare" (Latin for to keep watch).[3]

[1] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment – March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)
[2] ICH Harmonized Tripartite Guideline – Pharmacovigilance Planning E2E (Current Step 4 version – dated 18 November 2004)
[3] See the link: http://en.wikipedia.org/wiki/Pharmacovigilance

Since 2010, the European Union (EU) has introduced the concept of Pharmacovigilance System Mater File (PSMF) in its regulations and directives to ease and to harmonize the pharmacovigilance activities in the Member States of the European Union.[1,2]

Considering the importance of the European Union and the United States in producing highly qualified medicinal products around the world and their determining role in directing drug safety policies, make it important to compare those policies and to clarify the different aspects of pharmacovigilance activities and their characteristics in these two important members of International Conference on Harmonization (ICH).

In approach to the mentioned purposes, this master thesis will describe briefly the important characteristics of the Pharmacovigilance System in the European Union. After that, it will give a detailed account of the concept of Pharmacovigilance System Master File and its importance in the European Union. Then, it depicts the drug safety design in the United States and its comprising elements. At the end, it compares the characteristics of the two region's pharmacovigilance system, with specific emphasis on the newly introduced concept of pharmacovigilance system master file.

[1] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use)
[2] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 and Regulation (EC) No 1394/2007

The European Union Laws and Regulations

Pharmacovigilance System in the European Union

The European Union system of Pharmacovigilance acts at three different hierarchical levels. With regard to the pharmacovigilance, the European Medicine Agency (EMA) has the main tasks of the management of the Union pharmacovigilance database and data-processing network (the Eudravigilance Database), the coordination of safety announcements by the Member States, and the provision of information regarding safety issues to the public. At the second level, each Member State shall designate a Competent Authority for the performance of its pharmacovigilance tasks. Finally, the Marketing Authorization Holders (MAH) shall establish their own pharmacovigilance system equivalent to the relevant Member State's pharmacovigilance system, to ensure the monitoring and supervision of their authorized medicinal products and to take appropriate measures as necessary. They shall perform a regular audit of their pharmacovigilance system.[1,2]

In Europe, Directive 2001/20/EC, on the approximation of the laws, regulations and administrative provision of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, is the legal framework for obligations concerned with the monitoring of adverse reactions occurring in clinical trials. Therefore monitoring of those adverse reactions do not fall within the scope of pharmacovigilance activities and their guidelines.[3]

The pharmacovigilance system is defined in Article 1 (28d) of Directive 2001/83/EC, as amended by Directive 2010/84/EU, as "a system used by the marketing authorization holder and by Member States to fulfill the tasks and responsibilities listed in Title IX and

[1] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 and Regulation (EC) No 1394/2007.
[2] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use)
[3] Volume 9A of the rules governing medicinal products in the European Union (Final September 2008)

designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance".[1]

To achieve these goals, marketing authorization holders, the National Competent Authorities and the Agency should continuously validate and confirm safety signals, based on examination of information received from the individual case safety reports, aggregated data from active surveillance systems or studies, literature information and other data sources.[2] Furthermore, the Agency and the Competent Authorities ensure that marketing authorization holders implement, when appropriate, risk management plans to effectively monitor and manage risks associated with the safety of their medicinal products.[3] In order to gather information about safety signals and to reduce the risks of medicinal products, the pharmacovigilance system uses the following tools:

- **Individual Case Safety Report (ICSR):** Individual case safety reports shall be used for collection, processing, quality control, coding, classification, medical review and reporting suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time. The source for an individual case safety report could also be the literature, clinical study or post-authorization safety study[4] (those studies that are not covered by Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use[5]). In order to simplify the reporting of suspected adverse reactions, these reactions should only be reported to the Eudravigilance database.[6] Eudravigilance database, developed according to Article 24 of Regulation (EC) No 726/2004, is the Union pharmacovigilance database and data-processing network used to collect and collate pharmacovigilance information and ensures the simultaneous dissemination of information to the Competent Authorities on adverse reactions to medicinal

[1] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use)
[2] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
[3] Volume 9A of the rules governing medicinal products in the European Union (Final September 2008)
[4] Volume 9A of the rules governing medicinal products in the European Union (Final September 2008)
[5] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
[6] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use).

products authorized in the Community.[1] The marketing authorization holder shall submit information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day they gained knowledge of the event. Furthermore, the information on all non-serious suspected adverse reactions that occur in the Union will be submitted within 90 days following the day the marketing authorization holder gained knowledge of that event.[2]

- **Periodic Safety Update Report (PSUR):** The periodic safety update report shall focus on new information which has emerged since the data lock point of the last periodic safety update report and shall provide an accurate estimate of the population exposed to the medicinal product. These reports present the marketing authorization holder an opportunity to review the safety profile and the scientific evaluation of the risk-benefit balance of the medicinal product. Furthermore, these reports enable the marketing authorization holder to draw conclusions as to the need for changes and/or actions, including implications for the approved summary of product characteristics, package leaflet and labeling of the medicinal product. It also contains the result of assessments of effectiveness of risk minimization activities. The periodic safety update report shall be submitted electronically.[3,4]

  The marketing authorization holders of generic, well-established used, homeopathic or traditional-use herbal medicinal products submit periodic safety update report only if such obligation has been laid down as a condition of the marketing authorization or following the request of a Competent Authority based on pharmacovigilance concerns or lack of periodic safety update reports of an active substance after granting the marketing authorization. The frequency of the submission of the periodic safety update report shall be specified in the marketing authorization.[5]

[1] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 and Regulation (EC) No 1394/2007.

[2] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use).

[3] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC

[4] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use).

[5] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use).

- **Risk Management Plan:** Specifically, point (iaa) of Article 8(3) Directive 2001/83/EC, as amended by Directive 2010/84/EU constitutes the legal basis for implementation of the risk management plan for all marketing authorization application submitted after 2 (for centrally authorized medicinal products) / 21 (for authorized product through procedures other than the central procedure) July 2012, irrespective of their legal basis[1]. It shall contain characterization of the safety profile and an identification of the risks of the medicinal product and depicts all measures and interventions to prevent or minimize those risks and ascertains the effectiveness of the mentioned measures and interventions. The post-authorization obligations imposed as a condition of the marketing authorization are also documented in the risk management plan.[2,3] The holder of a marketing authorization granted before 21 July 2012 does not have to operate a risk management system if there are not concerns about the risks affecting the risk-benefit balance of an authorized medicinal product.[4] Furthermore, the submission of a risk management plant is not required for an application for a traditional use herbal medicinal product and homeopathic medicinal products registered through simplified registration.[5]

  The Risk Management Plan consists of the following parts:

  - **Part I:** Product overview;
  - **Part II:** The safety specification which should be a summary of the identified risks, important potential risks, and important missing information. It will form the basis of the evaluation of the need for risk minimization activities and, where appropriate, the risk minimization plan;
  - **Part III:** The Pharmacovigilance plan, which proposes actions to address the identified safety concerns and includes also the post-authorization safety studies.

[1] Question and Answers to support the implementation of the Pharmacovigilance legislation – Update, November 2012 (EMA/228816/2012)
[2] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use).
[3] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
[4] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use).
[5] Question and Answers to support the implementation of the Pharmacovigilance legislation – Update, November 2012 (EMA/228816/2012)

Routine pharmacovigilance activities will be sufficient, where no special safety concerns have arisen. But for medicinal products with important identified risks, important potential risks and important missing information additional pharmacovigilance activities are needed;

- **Post-Authorization Safety Studies:** These studies are non-interventional type and are initiated, managed or financed by the marketing authorization holder under obligations imposed by a National Competent Authority, the Agency or the Commission and involve the collection of data from patients or healthcare professionals and fall therefore outside of the scope of Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. The marketing authorization holder shall ensure that the protocols of the study are documented and are available for auditing and inspection. The marketing authorization holder shall send the abstracts and final study reports to the Member State in which the study was conducted[1,2];

- **Part IV:** Post-authorization efficacy studies: when previous efficacy evaluations have to be revised significantly, due to new understanding of the disease or the clinical methodology, the marketing authorization holder shall initiate and manage a post-authorization efficacy study[3];
- **Part V:** Risk minimization activities and an evaluation of the effectiveness of risk minimization activities;
- **Part VI:** Summary of the risk management plan, which consists of key elements of the risk management plan and the specific focus on risk minimization activities;
- **Part VII:** Annexes.[4]

[1] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
[2] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use)
[3] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use)
[4] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC

The new Title IX of Directive 2001/83/EC as amended by Directive 2010/84/EU states that as part of the pharmacovigilance system, the Marketing Authorization Holder shall:

a. have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance (QPPV);
b. maintain and make available on request a pharmacovigilance system master file;
c. operate a risk management system for all new marketing authorization applications and for holders of a marketing authorization granted before 21 July 2012 if there are concerns about the risks affecting the risk-benefit balance of their medicinal products;
d. 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 pursuant to Articles 21a, 22 or 22a of Directive 2001/83/EC, as amended;
e. 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.[1]

The previous Detailed Description of Pharmacovigilance System (DDPS) in the application for marketing authorization will be phased out in the determined transitional time to the Pharmacovigilance System Master File (PSMF) and thereafter, the module 1.8.1 of the application dossier for marketing authorization will contain a summary of the corresponding pharmacovigilance system including the following elements:

- proof that the applicant has at his disposal a Qualified Person responsible for Pharmacovigilance;
- the Member States in which the qualified person resides and carries out his/her tasks;
- the contact details of the qualified person;
- a reference to the location where the pharmacovigilance system master file for the medicinal product is kept;

[1] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use)

- the risk management plan and a summary thereof;
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfill the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.[1]

The applicant/MAH may combine this information in one single statement, signed by the applicant/MAH and QPPV. Irrespective of whether combined or not, the statement shall refer to the required wording as per Article 8(3)(ia) of Directive 2001/83/EC "the applicant has the necessary means to fulfill the tasks and responsibilities listed in Title IX of Directive 2001/83/EC". If available, the PSMF number assigned by the extended Eudravigilance Medicinal Product Dictionary (XEVMPD) should be included in the statement.[2]

[1] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use)
[2] Question and Answers to support the implementation of the Pharmacovigilance legislation – Update, November 2012 (EMA/228816/2012)

Pharmacovigilance System Master File (PSMF)

Definition and Legal Requirements

The definition of Pharmacovigilance System Master File is provided in Article 1(28e) of Directive 2001/83/EC, amended by Directive 2010/84/EU, as "A detailed description of the Pharmacovigilance (PV) system used by the marketing authorization holder with respect to one or more authorized medicinal products."[1] It encompasses all aspects of pharmacovigilance activities, including information on the tasks that have been subcontracted. The marketing authorization holder retains ultimate responsibility for compliance with the legal arrangements. The PSMF is going to be a document helping the appropriate arrangement and conducting of the marketing authorization holder's audits as well as being a tool for EU Qualified Person for Pharmacovigilance (QPPV) to maintain supervision over the PV System. The PSMF will be permanently available for inspection by the competent authority to verify compliance of all aspects of the pharmacovigilance system.[2]

The legal requirement for marketing authorization holder to maintain and make available upon request a Pharmacovigilance System Master File was described in Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 [Recitals (22) and (25)], amending Regulation (EC) No 726/2004 [Article 16 (4)] and Regulation (EC) No 1394/2007[3]; and Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 [Recitals (7) and (35)] amending Directive 2001/83/EC [Article 23(4), Article 104(3)(b)][4], to strengthen and rationalize the

[1] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use)
[2] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
[3] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 and Regulation (EC) No 1394/2007 (See also the endnotes)
[4] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use) (See also the endnotes)

monitoring of the safety of medicine products that have been placed on the market of the European Union (EU) and to harmonize the pharmacovigilance activities.[1]

Location

The PSMF will be stored in the Union either in a place, where the main pharmacovigilance activities of the MAH are done or at a site where the QPPV operates.[2] The MAH should have rational reasons for selection of its location. Following European Economic Area (EEA) agreement, the PSMF could be stored in Norway, Iceland or Lichtenstein. Where the main activities occur outside the Union or where no place could be determined for the main activities, the location of the PSMF is by default, at the site where the QPPV operates.[3] Details about the location of PSMF and information about any change of its location are required to be entered and immediately updated in the extended Eudravigilance Medicinal Product Dictionary (XEVMPD)[4] and on the European medicines web-portal.[5]

The pharmacovigilance system master file reference number is a unique code assigned by the Eudravigilance (EV) system, when the location information of PSMF with the format of Extended Eudravigilance Medicinal Product Report Message (XEVPRM) is entered. The applicant for a marketing authorization submits the location of pharmacovigilance system master file electronically and includes the pharmacovigilance system master file reference number in the application.[6,7]

[1] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
[2] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
[3] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012
[4] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012
[5] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 and Regulation (EC) No 1394/2007
[6] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012
[7] Question and Answers to support the implementation of the Pharmacovigilance legislation – Update, November 2012 (EMA/228816/2012)

The PSMF could be stored either in paper or in electronic form. It could be a virtual document, existing on different servers in the company or at suppliers of data services, but a clearly arranged printed copy will be directly available for inspection at the office address, where is mentioned in the summary of the pharmacovigilance system in the application for marketing authorization.[1]

The provisions in the new legislation about physical location of the pharmacovigilance system master file should been seen pragmatically in the light of modern technology where databases are spread on many international locations. The essential point is, that information will be readily available and comply with laws and regulatory provisions and that the PSMF can serve as a tool for the QPPV to have oversight of the Pharmacovigilance System.[2]

The MAH shall provide a copy of the PSMF on his cost within a 7 day time-frame if requested at any time by the National Competent Authority or the European Medicine Agency (EMA).[3,4] The request may entail the submission of a full PSMF or a part of it, as well as the history of changes or other relevant details.[5,6]

Even if the summary of PV system is not required, a PSMF must be available for all products after the transitional period. Specifically, applicants and marketing authorization holders of traditional herbal medicinal products (THMP) do not need to submit a summary of the PV system, but article 104 of Directive 2001/83/EC still applies

[1] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012

[2] See the link: http://www.ottosen.com/26-pharmacovigilance-system-master-file

[3] Article 23(4) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010)

[4] Article 16(4) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 (as as amended by the Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010)

[5] SME Workshop "Focus on Pharmacovigilance" – GVP Module II – Pharmacovigilance System Master File - Presented by Joanna Harper – Inspections, Enforcement & Standards Division (MHRA) – 19 April 2012

[6] Fourth Stakeholders Forum on the Implementation of the New Pharmacovigilance Legislation – Module II – Pharmacovigilance System Master File - Presented by Joanna Harper – Inspections, Enforcement & Standards Division (MHRA)

to them that a PSMF is needed to be made available and maintained.[1] The applicants and MAHs of the homeopathic medicinal products registered through simplified registration procedure do not have to operate a pharmacovigilance system, to include a PV system summary in their application and to maintain and make available a PSMF.[2]

Contents of the Pharmacovigilance System Master File

After implementation of the pharmacovigilance system master file a reduction in numbers of variations could be foreseen in comparison with the previous provision of Detailed Description of Pharmacovigilance System (DDPS). Changes to the contents of PSMF do not have to be notified to the Competent Authority and are not expected to require a 'variation' as part of the marketing authorization dossier, except for aspects covered by the article 8 of Directive 2001/83/EC with regards to changes to the summary of the pharmacovigilance system, including changes to the location of PSMF or the QPPV's name and his or her contact details. These changes should be immediately notified to the Agency and accordingly should be accompanied by an update of the Eudravigilance database and where necessary, an update of the European medicines web-portal.[3,4]

In order to introduce the pharmacovigilance system summary in the marketing authorization and accordingly the pharmacovigilance system master file at times other than the marketing authorization application or a renewal application, the MAH should submit a variation.[5,6] The classification of the variation will be defined in the revised variation classification guideline. Pending the publication of the revised variation classification guideline, the type of variation has been defined through a procedure in

[1] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012

[2] Question and Answers to support the implementation of the Pharmacovigilance legislation – Update, November 2012 (EMA/228816/2012)

[3] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC

[4] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012

[5] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012

[6] SME Workshop "Focus on Pharmacovigilance" – GVP Module II – Pharmacovigilance System Master File - Presented by Joanna Harper – Inspections, Enforcement & Standards Division (MHRA) - 19 April 2012

accordance the Article 5 of Regulation (EC) No 1234/2008[1] (based on the current legal provisions, introduction of the pharmacovigilance system summary or changes to the content of the summary of the PSMF could be accomplished through a variation type Ia_{IN} [2,3]). The variations could be grouped when more than one medicinal product are covered by a single pharmacovigilance system and therefore by a single PSMF.[4] The authorities are expected to waive the obligation of the current legal requirement for the DDPS when a company shifts to the new PSMF.[5]

A template for the PSMF is not provided[6], so companies will have flexibility as regards change control, as how the information is stored and retrieved.[7]

The minimum requirement for contents of the PSMF and its maintenance are set out in the Commission Implementing Regulation (IR) (EU) No 520/2012 on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC.[8]

The PSMF shall contain all of the information about:

1. Qualified Person for Pharmacovigilance (QPPV): including contact details, the curriculum vitae of the QPPV, the proof of his registration in Eudravigilance database and the description of the responsibilities of the QPPV to show his sufficient authority. There should be also a description of a back-up arrangement

[1] Question and Answers to support the implementation of the Pharmacovigilance legislation – Update, November 2012 (EMA/228816/2012)
[2] Pharmacovigilance System Master File (PSMF), QPPV and Audits - Federal Agency for Medicines and Health Products (FAMHP) – Presented by: Matthijs Nele – Bras – 15 May 2012
[3] Question and Answers to support the implementation of the Pharmacovigilance legislation – Update, November 2012 (EMA/228816/2012)
[4] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012
[5] Question and Answers to support the implementation of the Pharmacovigilance legislation – Update, November 2012 (EMA/228816/2012)
[6] Question and Answers to support the implementation of the Pharmacovigilance legislation – Update, November 2012 (EMA/228816/2012)
[7] Fourth Stakeholders Forum on the Implementation of the New Pharmacovigilance Legislation – Module II – Pharmacovigilance System Master File - Presented by Joanna Harper – Inspections, Enforcement & Standards Division (MHRA)
[8] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC

in the absence of the QPPV.[1] By demanding of a National Competent Authority a contact person for the pharmacovigilance issues shall be introduced at the national level and the PSMF shall contain the responsibilities of this person[2];

2. A description of the organizational structure of the MAH, depicting the position of the QPPV in the organization and the sites where different pharmacovigilance activities (including individual case safety report collection, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorization study management and management of safety variations) are undertaken;
3. A description of computerized systems and databases used to handle safety information and an assessment of their capabilities and their fitness for this purpose;
4. A description of sources of safety data and of data handling and recording for each of the pharmacovigilance activities including: risk-benefit monitoring, individual case safety report, periodic safety update report, risk management system, non-interventional studies, communicating of safety concerns with healthcare professionals and general public, and implementation of safety variations to the summary of product characteristics and package leaflet;
5. A description of the quality system for the pharmacovigilance activities, including the management of the human resources and record systems and the monitoring of compliance of the pharmacovigilance system to the obligations, conditions and timeliness imposed on marketing authorization;
6. A description of the subcontracted activities, where applicable.[3,4]

The PSMF should be written in English, unless the marketing authorization holder holds an approval in only one Member State, which in this case the EU official language of

[1] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC

[2] Article 104(4) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010)

[3] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC

[4] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012

that territory is also acceptable.[1] Contents of the PSMF have to be kept at least five years after the pharmacovigilance system has been formally terminated by the marketing authorization holder. When the marketing authorization ceases to exist, the pharmacovigilance data and documents have to be kept for at least 10 years.[2]

Contents of Annex of the Pharmacovigilance System Master File

Annex of the PSMF contains those components which will be subjected to continuous updating. Furthermore, presence of different detailed lists in the different PSMF sections is seen as a burden, if not moved to the Annex.[3]

The cover page of the annex points to the PSMF's reference number, the name of MAH and QPPV, the name of MAH sharing the pharmacovigilance system (as applicable), the list of other pharmacovigilance system master files of the MAH and the date of its preparation or its last update.[4]

Annex to the PSMF contains:

1. Annex A: the curriculum vitae of the QPPV and associated documents, lists of the QPPV's delegated activities and the persons, to whom are delegated;
2. Annex B: A list of contracts and agreements, including the subcontractors and copies of signed agreements;
3. Annex C: Lists of sources of safety data, including affiliates and third party contacts;
4. Annex D: A list of computerized systems and databases;
5. Annex E: Lists of written policies and procedures, for the specific quality system and processes to ensure:

[1] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012

[2] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC

[3] GVP – Key themes from the Public Consultation and next steps (Guideline on Good Pharmacovigilance Practices (GVP) – Comments from 'first wave' public consultation – Presented by: Priya Bahri (EMA) on behalf of the GVP Team

[4] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012

a. the continuous monitoring of pharmacovigilance data and risk minimization activities of the MAH;

b. scientific evaluation of the risks of medicinal products by the MAH;

6. Annex F: Lists of performance indicators used by the MAH and the results of performance assessment to continuously assure the good performance of pharmacovigilance activities;

7. Annex G: scheduled and completed audits and those associated with significant finding and unresolved notes (Marketing authorization holders shall perform regular audits of their pharmacovigilance system and shall place a note concerning the main findings of the audits on the pharmacovigilance system master file and ensure that an appropriate corrective action plan is prepared and implemented. The notes could be removed once corrective actions or sufficient improvement can be demonstrated.[1]);

8. Annex H: A list of all medicinal products covered by the PSMF and the name of Member State(s), in which the medicinal product is authorized (The list should be organized according to the active substances and shall point to the type of procedure for authorization and procedure number and presence of medicinal product on the market in the EU and other (non-EU) territories.);

9. Annex I: A logbook, which ensures that any changes in the contents of PSMF, made within the last 5 years, the person responsible for the alteration and the reason for that change (where appropriate) will be recorded (Changes in the QPPV's detailed information or other information described in the annex are excluded to be entered in this logbook[2]).[3,4,5]

[1] Article 104(2) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010)

[2] Article 5(4) of Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC

[3] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC

[4] Guideline on Good Pharmacovigilance Practices (GVP) Module II – Pharmacovigilance System Master File, 22 June 2012

[5] Pharmacovigilance System Master File (PSMF), QPPV and Audits - Federal Agency for Medicines and Health Products (FAMHP) – Presented by: Matthijs Nele – Bras – 15 May 2012

The Transitional Period

Marketing authorization holders of medicinal products authorized before **2 July 2012** through the centralized procedure have to maintain the PSMF and make it available on request on the date of their renewal or by the **end of 2 July 2015**, whichever is earlier. Marketing authorization holders of the products authorized before **21 July 2012** through procedures, other than the centralized procedure (through national procedure, Mutual Recognition Procedure or Decentralized Procedure), have to maintain and make available on request a PSMF on the date of their renewal or by the **end of 21 July 2015,** whichever is earlier.[1] (In Article 2 of Directive 2010/84/EU, the mentioned dates for maintenance and making available a PSMF for authorized products by procedures other than the centralized procedure are 21 July 2011 and end of 21 July 2014, respectively.[2])

In addition to the new applications for marketing authorization, the introduction of the summary of PV system applies in retrospect to medicinal products that undergo renewal after 2 (for authorized medicinal products through the centralized procedure) / 21 (for authorized medicinal products authorized through procedures other than the centralized procedures) July, 2012.[3]

[1] SME Workshop "Focus on Pharmacovigilance" – GVP Module II – Pharmacovigilance System Master File - Presented by Joanna Harper – Inspections, Enforcement & Standards Division (MHRA) - 19 April 2012
[2] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use)
[3] SME Workshop "Focus on Pharmacovigilance" – GVP Module II – Pharmacovigilance System Master File - Presented by Joanna Harper – Inspections, Enforcement & Standards Division (MHRA) - 19 April 2012

The American Laws and Regulations

The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBDR) of the United States' Food and Drug Administration (FDA) monitor and review safety information throughout a medicinal product's life cycle, from application for marketing authorization through approval of the application and after the drug is marketed.[1]

According to the section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) on new drugs, any person, who wants to introduce or deliver for introduction into interstate commerce any new drug, has to submit to the Secretary of Health and Human Services (the Secretary[2]) among the other information and as a part of the application the full reports of investigations, which have been made to show that such drug is safe and effective for use.[3]

During the premarketing phase, FDA's safety assessment of medicinal products was very intensive. In November 2004, FDA requested the Institute of Medicine (IOM) to study and conduct a complete review of FDA's post-market drug safety system, to strengthen its safety program for marketed medicinal products. The report, which issued in 2006, noted that FDA needed additional legal authorities and resources to effectively address safety issues of medicinal products.[4]

The Food and Drug Administration Amendments Act (FDAAA), which was signed into law in September 2007, provides for Title IX section 901 and has greatly enhanced FDA's authorities regarding post-market's safety of drugs. Among the others, it provides FDA with the authority to require labeling changes, if new safety information becomes available that the Agency (the US Food and Drug Administration) believes should be included in the labeling of the drug. The responsible person for new drugs, or if the reference drug is not currently marketed, the holder of an approved abbreviated new drug application (i.e. a generic medicinal product) shall submit within 30 days a

[1] Advances in FDA's Safety Program for Marketed Drugs (Center for Drug Evaluation and Research) – April 2012
[2] CFR - Title 21 § 310.3; CFR - Title 21 § 600.3,
[3] Federal Food, Drug and Cosmetic Act, Chapter V, Subchapter A, Section 505 (21 USC 355)
[4] Advances in FDA's Safety Program for Marketed Drugs (Center for Drug Evaluation and Research) – April 2012

supplement proposing changes to the approved labeling to reflect the new safety information.[1] "New Safety Information" is described as information derived from an adverse event report, a post-approval study (including a study under section 505(o)(3) of title 21 of Food and Drug Acts), a clinical trial, peer-reviewed biomedical literature, data derived from the post-market risk identification and analysis system (under section 505(k) of the Act), or other scientific data, which the Agency has become aware of and finds appropriate regarding a serious risk or an unexpected serious risk associated with use of the drug.[2] Subparagraph (4) of section 505(o) of the Act also imposes time frames for FDA staff to review the response of the responsible person to FDA's notification, and gives FDA new enforcement tools to bring about timely and appropriate safety labeling changes.[3] Prior to FDAAA, FDA did not have the authority to order such label changes if the responsible person did not voluntarily make the changes.[4]

The FDAAA also gives FDA the authority to require certain post-marketing studies and clinical trials for new drugs approved under section 505 of the Food, Drug and Cosmetic Act or for biological medicinal products approved under section 351 of the Public Health Service Act (the PHS Act) (Title 42 of section 262 U.S.C.).[5] Under the new authority, any person who has submitted to the Secretary a pending covered application or is the holder of an approved covered application for new drugs[6] or for biological medicinal products[7] has to conduct a post-approval study or studies or a post-approval clinical trial or trials of the drug, when the Secretory on the basis of scientific data related to the use of the drug finds it appropriate to assess a known serious risk or signals of a serious risk, or to identify an unexpected serious risk when available data indicates its potential. The Secretary may not require the responsible person to conduct a post-approval study, unless the Secretary determines that the reports of clinical experience and other data obtained by the responsible person with respect to the new drug or abbreviated new drug or the information received by the active post-market risk identification (under

[1] Federal Food and Drug Administration Amendment Act (FDAAA) of 2007
[2] Federal Food, Drug and Cosmetic Act, Chapter V, Subchapter A, Section 505-1 (b) (21 USC 355-1)
[3] Regulatory Summary - Pharmacovigilance & Risk Management (United States) IDRAC 34595 – Thomson Reuters
[4] Advances in FDA's Safety Program for Marketed Drugs (Center for Drug Evaluation and Research) – April 2012
[5] Regulatory Summary - Pharmacovigilance & Risk Management (United States) IDRAC 34595 – Thomson Reuters
[6] Under the meaning subsection (b) of Federal Food, Drug and Cosmetic Act, Chapter V, Subchapter A, Section 505 (21 USC 355)
[7] Under the meaning of Public Health Service act – Section 351

subsection (k)(3) of § 355 of Title 21 of Food and Drug Act) will not be sufficient to assess a known serious risk or signals of a serious risk or to identify an unexpected serious risk. Similarly, the Secretary may not require the responsible person to conduct a clinical trial, unless the Secretary makes a determination that a post-approval study or studies will not be sufficient to gain the above mentioned information.[1] Prior to FDAAA, these studies were conducted as voluntary commitments by manufacturers.[2]

In the context of the Prescription Drug User Fee Act (PDUFA) III, on June 12, 2002, FDA agreed to issue guidance for industry to cover the different phases of the risk assessment and risk management[3] The same classification would be used here to explain the different parts of the pharmacovigilance system in the United States:

1. Guidance for Premarketing risk assessment

The sponsor is responsible for promptly reviewing all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any sources, foreign or domestic sources, or from any clinical or epidemiological investigation, or from animal or in vitro studies.[4]

The sponsor is responsible for notifying FDA and all participating investigators in a written Investigational New Drug (IND) safety report of all serious and unexpected serious risk from clinical trials or any other sources that has not previously been reported to the Agency by the sponsor. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.[5]

Each written IND safety notification must be submitted electronically or on an FDA Form 3500A or in a narrative format. Foreign events may be submitted either on an FDA Form 3500A or if preferred on a Council for International Organization of Medical

[1] Federal Food and Drug Administration Amendment Act (FDAAA) of 2007
[2] Advances in FDA's Safety Program for Marketed Drugs (Center for Drug Evaluation and Research) – April 2012
[3] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)
[4] CFR - Title 21 § 312.32 (b) (see also the endnotes)
[5] CFR - Title 21 § 312.32 (c)(1)

Science (CIOMS) I form. Reports from animal, in vitro, clinical or epidemiological studies shall be submitted in a narrative format and shall bear prominent identification of its contents, i.e., "IND Safety Report" and must be transmitted to the FDA's responsible center for review of the IND, i.e. review division in CDER or in CBER.[1]

The sponsor shall provide all relevant follow up information it has obtained regarding the investigational drug in a "Follow up IND Safety Report".[2]

The sponsor shall submit a report of the progress of the investigations within 60 days of the anniversary date that the IND went into effect. This report includes a summary of all IND safety reports submitted during the last year and a description of any changes in the investigator brochure.[3]

2. Guidance for Post-marketing Pharmacovigilance and Pharmacoepidemiologic Assessments

The Pharmacovigilance in the United States encompasses all scientific and data gathering activities relating to the detection, assessment, and evaluation of safety signals and includes:

- **A.** Safety signal identification,
- **B.** Pharmacoepidemiologic assessment and safety signal interpretation
- **C.** Pharmacovigilance plan development. [4]

A. Safety signal identification:

The FDA's existing post-marketing safety reporting requirements for human drugs and biological products can be found under Title 21 of Code of Federal Regulation (CFR) parts 310.305, 314.80, 314.98, 600.80, 1271.350 and Section 760 of the Food Drug and Cosmetic Act (FDCA), as amended by Public Law 109-462.[5]

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[1] CFR - Title 21 § 312.32 (c)(v)
[2] CFR - Title 21 § 312.32 (d)
[3] CFR - Title 21 § 312.33
[4] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)
[5] Post-Marketing Surveillance and Epidemiology: Human Drug and Therapeutic Biological Products – Food and Drug Administration - December 15, 2012; and See the link: http://www.fda.gov/Drugs/DrugSafety/ucm299833.htm

Manufacturers, packers, distributors and Applicants having an approved New Drug Application (NDA)[1] or an approved Abbreviated New Drug Application (ANDA)[2], or an approved Biologic License Application (BLA)[3] must promptly review and submit to FDA information of all adverse experiences to the medicinal product, obtained or otherwise received, regardless of the source of the information. Applications must also submit all follow up information on such reports to FDA.[4]

Furthermore, Manufacturers, packers and distributors of marketed prescription drug products that are not subject of an approved new drug or abbreviated new drug application have to maintain records and make reports to FDA of all serious, unexpected adverse drug experiences associated with the use of their products and their related follow-up reports.[5]

Manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/P's), which are regulated solely under section 361 of the Public Health Service Act have to investigate any adverse reaction involving a communicable disease related to the HCT/P that they make available for distribution. Each severe adverse reaction has to be reported to FDA on a Form FDA-3500A within 15 calendar days of initial receipt of the information. Follow-up reports to these 15-day reports will be submitted by the manufacturer within 15 calendar days of the receipt of new information or as requested by FDA.[6]

Prior to the enactment of Public Law 109-462, only Over the Counter (OTC) drugs marketed with an approved application were subject to mandatory post-marketing safety reporting requirements. Under the Dietary Supplement and Nonprescription Drug Consumer Protection Act, on December 22, 2006, which became mandatory in December 2007 and amended the Federal FDCA, the manufacturer, packer or distributor whose name appears on the label of a nonprescription drug without an approved application marketed in the United States have to submit any report received

[1] CFR - Title 21 § 314.80
[2] CFR - Title 21 § 314.98
[3] CFR - Title 21 § 600.80
[4] CFR - Title 21 § 314.80(b)
[5] CFR - Title 21 § 310.305
[6] CFR – Title 21 §§ 1271.1, 1271.10, 1271.330, 1271.350,

of serious adverse events associated with such drugs to the Agency within 15 business days.[1] Serious adverse event reports for nonprescription human drug products marketed without an approved application could be submitted on paper or in the electronic format.[2]

Several types of post-marketing adverse experience reports are as following:

a. The 15-day Alert Report: The 15-day Alert Report or the "expedited post-marketing Report" and "Post-marketing 15-day Alert reports – follow up" must be filed for all serious and unexpected adverse experiences to drug or non-vaccine biologics, using FDA Form 3500A or the FDA's electronic system.[3] For nearly 35 years, FDA has received the post-marketing safety reports on paper. Although current regulations do not use the term Individual Case Safety Report (ICSR), the term is used in FDA and ICH guidance to refer to the adverse drug experience information supplied on the FDA Form 3500A or other approved forms.[4] Since 2000, FDA has accepted electronic submissions of ICSRs with XML format.[5] Data from both electronic and paper reports are entered into the FDA's Adverse Event Reporting System (FAERS) database. FAERS is a computerized information database designed to support FDA's post-marketing safety surveillance program for drug and biological products[6]. The content of FDA's electronic format is equivalent in all elements of information to those specified in FDA Form 3500A and is approved in advance by the FDA Medical Products Reporting Program (MedWatch).[7]

[1] Post-Marketing Surveillance and Epidemiology: Human Drug and Therapeutic Biological Products – Food and Drug Administration - December 15, 2012
[2] Section 760 of the FDCA and See the link: https://www.federalregister.gov/articles/2009/08/21/E9-19682/postmarketing-safety-reports-for-human-drug-and-biological-products-electronic-submission
[3] CFR - Title 21 § 314.80(c)(2)(f)
[4] See the link: https://www.federalregister.gov/articles/2009/08/21/E9-19682/postmarketing-safety-reports-for-human-drug-and-biological-products-electronic-submission
[5] See the link: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm
[6] See the link: https://www.federalregister.gov/articles/2009/08/21/E9-19682/postmarketing-safety-reports-for-human-drug-and-biological-products-electronic-submission
[7] CFR - Title 21 § 310.305 (d)

Adverse experience reports to vaccines have to be submitted to the FDA's Vaccine Adverse Event Reporting System (VAERS), which is a computerized database designed to post-marketing surveillance program for vaccine products. The adverse reports of vaccines can be submitted on a VAERS paper form or electronically using the VAERS web-based system. Foreign serious and unexpected events (including those associated with the use of vaccines) will be filed using the FDA Form 3500A or the International Organizations of Medical Sciences (CIOMS) I form, introduced by the World Health Organization (WHO).[1,2]

To avoid duplication of reports, manufacturers, packers and distributors of drug and biological products having an approved application may submit all reports of serious adverse drug experiences to the responsible person within 5 calendar days of receipt of the report instead of to FDA. Similarly, packers and distributors of prescription drug products marketed without an approved application may meet their post-marketing 15-day safety reporting obligations by submitting all reports of serious adverse drug experiences to the manufacturers within 5 calendar days of the receipt of the information instead of to FDA. Manufacturers of drugs marketed without an approved application are not required to submit post-marketing periodic safety reports to FDA.[3]

b. Periodic Adverse Drug Experience Report or Periodic Adverse Experience Report: The Applicant are required to report every adverse event not reported in a 15-day Alert report (including all serious expected and non-serious events) at quarterly intervals for three years following application approval and annually thereafter in Periodic Adverse Drug Experience Report or Periodic Adverse Experience Report.[4]

[1] CFR - Title 21 § 314.80(c)(2)(f) and CFR - Title 21 § 600.2
[2] See the link: https://www.federalregister.gov/articles/2009/08/21/E9-19682/postmarketing-safety-reports-for-human-drug-and-biological-products-electronic-submission
[3] See the link: https://www.federalregister.gov/articles/2009/08/21/E9-19682/postmarketing-safety-reports-for-human-drug-and-biological-products-electronic-submission
[4] CFR - Title 21 § 314.80(c)(2)(i) and CFR – Title 21 § 600.80

Each periodic report must contain the following parts and each part may be submitted electronically or on paper[1]:

1. A narrative summary and analysis of information contained in the report and an analysis of all 15-day Alert reports submitted during the reporting interval;
2. FDA Form 3500A for each adverse event not filed under a 15-day Alert report. Foreign events have to be reported either on Form 3500A or on a CIOMS I form;
3. A description of actions taken since the last report as a result of adverse event experiences.[2]

The summary, the analysis and history of actions are submitted to the Agency in a narrative format.[3]

c. NDA Field Alert Report: Within 3 working days, the Applicant shall submit to the FDA information about any incidents due to medication errors or any information due to bacteriological contamination or any other significant chemical, physical or other changes of distributed drug products.[4]

d. Annual Report: Each year within 60 days of the anniversary date of application approval, the applicant shall submit an annual report to the FDA division responsible for reviewing of the application. It contains all new significant information on safe and effective use of the medicinal product, which the applicant has received or otherwise obtained during the annual reporting intervals.[5]

B. Pharmacoepidemiologic assessment and safety signal interpretation: Safety signals important enough to warrant additional investigation could be further evaluated by the following non-randomized observational studies:

[1] See the link: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm
[2] CFR - Title 21 § 314.80(c)(2)(ii)
[3] See the link: https://www.federalregister.gov/articles/2009/08/21/E9-19682/postmarketing-safety-reports-for-human-drug-and-biological-products-electronic-submission
[4] CFR - Title 21 § 314.81
[5] CFR - Title 21 § 314.81

a. pharmacoepidemiologic studies;

b. registries;

c. surveys.[1]

a. Pharmacoepidemiologic studies: A pharmacoepidemiologic study could be used prior to the marketing to study the natural history of disease or pattern of product use, or to estimate background rates of adverse events. But, more often, they are initiated post-approval, when a safety signal has been identified. Unlike a case series, these studies have a protocol and a control group and test pre-specified hypotheses and can allow for the estimation of the relative risk of an outcome associated with a product.

b. Registries: A registry is an organized system for collection, storage, retrieval, analysis and dissemination of information on individual persons exposed to a specific medical intervention, who have either a particular disease or condition and prior exposure to substances known or suspected to cause adverse health effects. Whenever possible, a control or comparison group with the same diseases or conditions and without any exposure to the susceptible substances should be included.

Registries are particularly helpful for:

1. Collecting outcome information not available in large automated databases; and
2. Collecting information from multiple sources, e.g. physician records, hospital summaries, pathology reports or vital statistics.

c. Surveys: Sponsors could gather information through patient or health care provider surveys based on a written protocol. FDA recommends that sponsors should consider, whether translation and cultural validation would be important in gathering information.[2]

[1] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)

[2] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)

C. Pharmacovigilance plan development

The term “Pharmacovigilance Plan” is defined differently in the ICH draft E2E document, as by the FDA. The ICH E2E Pharmacovigilance Planning guidance indicates that a pharmacovigilance plan would be routinely developed (i.e., even when a sponsor does not anticipate that enhanced pharmacovigilance efforts are necessary). But FDA suggests that for most products, routine pharmacovigilance (i.e. compliance with applicable post-marketing reporting requirements under FDCA and FDA regulations) is sufficient for post-marketing risk assessment. FDA believes pharmacovigilance plans may be appropriate when serious safety risks have been identified pre- or post-approval, or at risk populations have not been adequately studied.[1]

A pharmacovigilance plan may be developed by itself or as part of a Risk Minimization Action Plan (RiskMAP).[2] The pharmacovigilance plan can be developed during product development prior to approval of a new product, or when a safety concern arises in the post-marketing period.[3]

Furthermore, sponsors have the opportunity to develop a stand-alone document for regions that prefer this approach or to incorporate elements of the safety specification and pharmacovigilance plan into the Common Technical Document (CTD).[4]

A pharmacovigilance plan could include one or more of the following elements:

- **a.** Submission of specific serious adverse events reports in an expedited manner beyond routine required reporting (i.e, as 15-day reports);
- **b.** Submission of adverse event report summaries at more frequent pre-specified intervals;
- **c.** Active surveillance that could be: A. drug based, B. setting based, or C. event based;

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[1] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)and see the link: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm161051.htm

[2] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)

[3] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)

[4] International Conference on Harmonization (ICH) guidance E2E: pharmacovigilance Planning (April 2005)

d. Additional pharmacoepidemiologic studies;

e. Creation of registries or implementation of patient or health care provider surveys;

f. Additional controlled clinical trials.[1]

Structure of the Pharmacovigilance Plan:

1. Summary of Ongoing Safety Issues;

2. Routine Pharmacovigilance Practices for all medicinal products, that include:

   - Systems and processes that ensure that information about all suspected adverse reactions reported to the personnel of the company are collected and collated in an accessible manner;

   - The preparation of reports for regulatory authorities: 1. Expedited adverse drug reaction reports and Periodic Safety Update Reports (PSUR);

   - Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labeling and liaison with regulatory authorities;

   - Other requirements, as defined by local regulations;

3. Action Plan for Safety Issues;

4. Summary of Actions to be completed, including Milestones.[2]

Sponsors may meet with representatives from the appropriate Office of New Drugs review division and the Office of Drug Safety in CDER, or the appropriate Product Office and the Division of Epidemiology, Office of Biostatistics and Epidemiology in CBER regarding the specifics of a given product's pharmacovigilance plan.[3] During the marketing of the medicinal product, any important emerging information about benefit or

[1] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)
[2] International Conference on Harmonization (ICH) guidance E2E: pharmacovigilance Planning (April 2005)
[3] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)

risk of the medicinal product should be discussed and may result in re-evaluation of the pharmacovigilance plan. Furthermore, the sponsor should evaluate the effectiveness of the pharmacovigilance plan and make a revision to it, when it seems necessary.[1]

3. Guidance for Development and implementation of Risk Minimization Action Plans (RiskMAP)[2]

Before FDAAA was enacted, FDA approved a small number of drug and biological products with Risk Minimization Action Plans (RiskMAP), which is a safety program designed to minimize known risks of a product, while preserving its benefits. implementing regulations establish requirements for routine risk assessment and risk minimization. For the majority of approved products, routine reporting requirements and incorporation of appropriate product labeling were adequate for risk minimization and benefit preservation. In rare instances, when additional measures were needed to ensure that the benefits of a drug outweigh the risks of the drug, FDA approved the drug with a RiskMAP and the sponsor had to consider implementing a RiskMAP.[3,4]

Risk Management Plan/Risk Evaluation and Mitigation Strategies (REMS)

Under FDAAA, FDA has authority to require manufacturers to implement special risk management programs, called Risk Evaluation and Mitigation Strategies (REMS).[5] If the Secretary, in consultation with the office responsible for reviewing the drug and the office responsible for post-approval safety of the drug, determines that a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug outweigh the risks of it, then the applicant having an approved application for new drug or for abbreviated new drug or for a biological medicinal product has to submit a REMS. The proposed REMS must be submitted within 120 days of the FDA notification for the

[1] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)
[2] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)
[3] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)
[4] Guidance for Industry – Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and proposed REMS modifications – U.S. Department of Health and Human Services Food and Drug Administration – September 2009
[5] Advances in FDA's Safety Program for Marketed Drugs (Center for Drug Evaluation and Research) – April 2012

REMS submission or within another reasonable time as FDA determines for the protection of public health. The responsible person has to maintain compliance with the requirements of the approved strategy or with other requirements regarding assessments of approved strategies.[1]

Risk Assessment and risk minimization form together, what FDA calls Risk Management. Risk Management is an iterative process throughout a product's lifecycle and consists of:

A. Assessing a product's benefit-risk balance;
B. Developing and implementing tools to minimize its risks while preserving its benefits;
C. Evaluating tool effectiveness and reassessing the benefit-risk balance;
D. Making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance.[2,3]

[1] Federal Food and Drug Administration Amendment Act (FDAAA) of 2007 (see also the endnotes)
[2] Regulatory Summary - Pharmacovigilance & Risk Management (United States) IDRAC 34595 – Thomson Reuters
[3] Guidance for Industry - Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment - March 2005 (U.S. Department of Health and Human Services Food and Drug Administration)

Discussion

In both the European Union and the United States, pharmacovigilance activities cover the whole life-cycle of medicinal products for human use. The full safety profile of medicinal products can only be known after marketing of the products and in this period, pharmacovigilance activities become especially important for the protection of public health.

The European Medicine Agency and the National Competent Authorities in the European Union and the Food and Drug Administration in the United States are empowered to impose certain obligations on authorized medicinal products, to ensure the appropriate changes to medicinal product's labeling and to conduct post-authorization safety studies, when new safety information make them necessary. The pharmacovigilance system in both areas demand expedited and obligational recording and reporting of all available data about the serious unexpected adverse events, medication errors and any suspected transmission of an infectious agent through the medicinal products.

According to the Article 57(1)(d) of Regulation (EC) No 726/2004, the European Medicine Agency has created a permanently accessible electronic database (the Eudravigilance Database) for collection, collation and dissemination of information on suspected adverse reactions to medicinal products for human use authorized by the Union. The Eudravigilance database is equipped to immediately forward reports on suspected adverse reactions received from marketing authorization holders to the Member States, on whose territory the reaction occurred.

In the United States, FDA's Adverse Event Reporting System (FAERS) and FDA's Vaccine Adverse Event Reporting System (VAERS) are computerized information databases designed to support FDA's post-marketing safety surveillance program for drugs and biological products and for vaccines, respectively.

In the European Union, the safety reports have to be submitted only electronically. Under the regulations and laws on safety in the United States, the responsible person of an application or the manufacturers, packers and distributors currently can submit the

safety reports in paper or electronically. By the way, FDA is also proposing rules to make the electronic submission, the mandatory format for post-marketing safety reports.

According to Directive 2010/84/EU, amending Directive 2001/83/EC and as a result of the submission of all suspected adverse reaction data directly to the Eudravigilance database, the periodic safety update report does not work anymore as a detailed listing of individual case safety reports. The submission of periodic safety update report is also exempted for marketing authorization holders of generic, well-established used, homeopathic or traditional-use herbal medicinal products, unless such obligational submission has been laid down as a condition for the marketing authorization or following the request of a Competent Authority based on pharmacovigilance concerns or lack of periodic safety update reports of an active substance after granting the marketing authorization.

Under Title 21 of Code of Federal Regulation (CFR) §§ 314.80, 314.98, 600.80, periodic reports shall contain among other data, information about all serious expected and non-serious adverse events, which are not reported through the post-marketing “15-day Alert reports” or their follow-up reports. These periodic reports also include a narrative summary of the information in the report and an analysis of the “15-day Alert reports” submitted during the reporting intervals.

With regard to the “pharmacovigilance plan”, the ICH and the FDA have different views. ICH E2E guideline on Pharmacovigilance Planning suggests that a “pharmacovigilance plan” would routinely be developed, even when the sponsor does not anticipate that enhanced pharmacovigilance efforts are necessary. But in the United States, for most products routine pharmacovigilance activities (i.e. compliance with applicable post-market requirements under the FDCA and FDA implementing regulations) will be sufficient for post-marketing surveillance and risk assessment, and a pharmacovigilance plan describes pharmacovigilance efforts beyond the routine post-marketing spontaneous reporting, and is designed to enhance and expedite the sponsor’s acquisition of safety information. The sponsors have to develop a pharmacovigilance plan for products for which: (1) serious safety risks have been identified post-approval

and/or already identified safety risks need more evaluation, or (2) at risk populations have not been adequately studied.

Under FDAAA of 2007, if FDA believes that a risk evaluation and mitigation strategy (REMS) is necessary to assure that the drug's benefits outweigh its risk, the manufacturers have to implement a REMS for the drug.

But in the European Union, the marketing authorization holders shall operate a risk management system after 2 July 2012 for each centrally authorized medicinal product and after 21 July 2012 for medicinal products authorized through national procedure, MRP and DCP. The medicinal products authorized before 2 July (for centrally authorized) and 21 July 2012 (for authorization through national procedure, MRP, MCP) are not obliged to operate a risk management system, if there are no concerns about the risks affecting the risk-benefit balance of the medicinal product. However, the medicinal products with active substances, biosimilars, medicinal products for pediatric use and medicinal products involving a significant change in the marketing authorization, including a new manufacturing process of a biotechnologically derived medicinal product have to implement a risk management system.[1,2]

The extent of measures included in the pharmacovigilance plan and in the risk management system in both the US and the EU systems should be proportionate to the identified risks, the potential risks and the missing information.

In the European Union, the Regulation (EU) No 1235/2010 and the Directive 2010/84/EU have introduced the concept of Pharmacovigilance System Master File (PSMF), as a detailed description of the pharmacovigilance system used by the marketing authorization holder for one or more authorized medicinal products. The PSMF is aimed to strengthen and rationalize the monitoring of safety information of the medicinal products, which are placed on the market of the European Union and to harmonize the pharmacovigilance activities throughout the EU.

[1] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use)
[2] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 (amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 and Regulation (EC) No 1394/2007

Type of Medicinal Product	Requirement for a Pharmacovigilance System	Requirement for the location of the PSMF in the Application	Requirement for a Risk Management System	Requirement to submit a Risk Management Plan
Traditional Herbal Medicinal Product	Applies	Does Not Apply	Applies	Does Not Apply
Other Herbal Medicinal Products	Applies	Applies	Applies	Applies
Homeopathic Simplified Registration	Does Not Apply	Does Not Apply	Does Not Apply	Does Not Apply
Other Homeopathic Medicinal Products	Applies	Applies	Applies	Applies

Pharmacovigilance System Master File (PSMF), QPPV and Audits - Presented by: Matthijs Nele[1]

After 2 July 2012 (for centrally authorized medicinal products) and 21 July 2012 (for nationally authorized medicinal products and medicinal products authorized through Mutual Recognition and Decentralized Procedures) and at the time of submission of an initial application, applicants have to include a summary of their pharmacovigilance system in their marketing authorization application.

For medicinal products authorized before 2 July 2012 (for centrally authorized products) and 21 July 2012 (for nationally authorized products or for products authorized through MRP or DCP), the marketing authorization holders have to include a summary of their pharmacovigilance system in their marketing authorization application:

- At the time of the annual renewal for a conditional marketing authorization through the centralized procedure,
- At the time of marketing authorization's renewal
- by 2 (for centrally authorized products) / 21 (for non-centrally authorized products) July 2015.[2]

Among other documents, the pharmacovigilance system master file also contains a description of sources of safety data and a recording for each individual case safety

[1] Pharmacovigilance System Master File (PSMF), QPPV and Audits - Federal Agency for Medicines and Health Products (FAMHP) – Presented by: Matthijs Nele – Bras – 15 May 2012

[2] Question and Answers to support the implementation of the Pharmacovigilance legislation – Update, Novermber 2012 (EMA/228816/2012)

report and periodic safety update report. The content of the PSMF has to be kept at least five years after the pharmacovigilance system has been formally terminated by the marketing authorization holder. When the marketing authorization ceases to exist, the pharmacovigilance data and documents have to be kept for at least 10 years.[1]

Even though the concept of the pharmacovigilance system master file and its particulars and characteristics are newly introduced in the EU's regulation and directives, there are some similar provisions in FDA Code of Federal Regulation, which demand from the applicants having approved new drug applications or approved abbreviated new drug applications and from manufacturer having licensed biologic applications to archive and retain records of all adverse events, known to them, including raw data and any correspondence relating to adverse drug experience. These records shall be maintained for a period of 10 years. If an applicant or licensed manufacturer fails to establish and maintain records and make reports, as required, FDA may withdraw the approval of the application or the license and prohibits continued marketing of the drug product or the biological product that are subject of the application or the license, respectively.[2]

Besides, each manufacturer, packer and distributor of a nonprescription drug without an approved application or of a marketed prescription drug not subject of an approved NDA or ANDA have to establish and maintain records of all serious and unexpected adverse drug experience associated with the use of their products. The data shall be maintained in a file along with other written complaints involving the possible failure of the drug product to meet any of its specifications. The file shall be maintained at the establishment where the drug product involved was manufactured, processed or packed, or may be maintained at another facility if the written records in such files are readily available for inspection at that facility.[3] Any authorized FDA employee, at all reasonable times, shall have access to the records and can copy and verify the records established and maintained under this section.[4]

[1] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 (on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
[2] Titel 21 Chapter I, CFR §$ 314.80, 314.98, 600.80
[3] Title 21 Chapter I, CFR §§ 211.198, 310.305
[4] Title 21 Chapter I, CFR § 310.305

Summary

The decision of approving a medicinal product is based on its satisfactory balance between benefits and risks within the conditions specified in the product's labeling. Due to the nature and limited duration of premarketing evaluations and investigations, the full safety profile of medicinal products can only be known after marketing of the products. The continuously expanding drug safety information in the post-marketing phase, make it necessary for marketing authorization holders to systematically collect and collate their safety information and to update their corresponding pharmacovigilance activities.

Under the previous provision of Detailed Description of Pharmacovigilance System (DDPS) in the European Union, the marketing authorization applications contained the whole safety information and pharmacovigilance data and the marketing authorization holders (MAH) had to submit the variations to implement the needed changes in their pharmacovigilance information. In 2010, the European Union has introduced the concept of Pharmacovigilance System Mater File (PSMF) in its regulations and directives, to ease and to harmonize the procedure of pharmacovigilance activities in the European Community and to reduce the number of unnecessary variations to the marketing authorizations. The DDPS will be gradually phased out to the PSMF. By the transitional time of 2 (for centrally authorized products)/ 21 (for products authorized through other procedures) July 2015, MAH have already maintained and made available on request a PSMF for their authorized medicinal products.

In FDA Code of Federal Regulation, there are some provisions for mandatory archiving and retaining records of adverse reactions to various groups of medicinal product. These records have to be kept in a file and should be ready for inspection by the authorized FDA employees. These provisions show some rudimentary similarities to the concept of pharmacovigilance system master file and its characteristics in the regulations and directives of the European Union.

A better understanding of the specifications of the pharmacovigilance system in the European Union and the United States and a comparison between the two systems would be the aim of this master thesis.

Endnotes

- Recital (22) of Regulation (EU) No 1235/2010: It is appropriate to strengthen the supervisory role for medicinal products for human use authorized through the centralized procedure by providing that the supervisory authority for pharmacovigilance should be the competent authority of the Member State in which the pharmacovigilance system master file of the marketing authorization holder is located.
- Recital (25) of Regulation (EU) No 1235/2010: The pharmacovigilance activities provided for in this Regulation require that uniform conditions be established as concerns the contents and maintenance of the pharmacovigilance system master file, as well as the minimum requirements for the quality system for the performance of pharmacovigilance activities by the Agency, the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities, and the minimum requirements for the monitoring of the data contained in the Eudravigilance database to determine whether there are new risks or whether risks have changed.
- Article 16(4) of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010: The Agency may at any time ask the marketing authorization holder to submit a copy of the pharmacovigilance system master file. The marketing authorization holder shall submit the copy at the latest 7 days after receipt of the request.
- Recital (7) of Directive 2010/84/EU: The marketing authorization holder should establish a pharmacovigilance system to ensure the monitoring and supervision of one or more of its authorized medicinal products, recorded in a pharmacovigilance system master file which should be permanently available for inspection. The competent authorities should undertake to supervise those pharmacovigilance systems. Applications for marketing authorizations should therefore be accompanied by a brief description of the corresponding pharmacovigilance system, which should include a reference to the location where the pharmacovigilance system master file for the medicinal product concerned is kept and available for inspection by the competent authorities.
- Recital (35) of Directive 2010/84/EU: The pharmacovigilance activities provided for in this Directive require that uniform conditions be established as concerns the contents and maintenance of the pharmacovigilance system master file, as well as the minimum requirements for the quality system for the performance of pharmacovigilance activities by the national competent authorities and marketing authorization holders, the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities, and the minimum requirements for the monitoring of the data contained in the Eudravigilance database to determine whether there are new risks or whether risks have changed.
- Article 23(4) of Directive 2001/83/EC as amended by Directive 2010/84/EU: The national competent authority may at any time ask the marketing authorization holder to submit a copy of the pharmacovigilance system master file. The marketing authorization holder shall submit the copy at the latest 7 days after receipt of the request.

- Article 104(3) of Directive 2001/83/EC as amended by Directive 2010/84/EU: As part of the pharmacovigilance system, the marketing authorization holder shall: (b) maintain and make available on request a pharmacovigilance system master file;
- Code of Federal Regulation - Title 21 § 312.32 (b) Review of safety information: The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.
- Federal Food and Drug Administration Amendment Act (FDAAA) Title IX – Section 901, as amending Section 505 (p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 355): A person may not introduce or deliver for introduction into interstate commerce a new drug if:

  A)(i) the application for such drug is approved under subsection (b) (i.e. New Drug Application) or (j) (i.e. Abbreviated New Drug Application) of § 355 and is subject to section 503(b) (review of television advertisement law under); or (ii) the application for such drug is approved under section 351 of the Public Health Service Act (for biological products);

  and

  (B) a risk evaluation and mitigation strategy is required under section 505-1 with respect to the drug and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under section 505-1, including requirements regarding assessments of approved strategies.

- Federal Food and Drug Administration Amendment Act (FDAAA) Title IX – Section 901, as amending Section 505-1 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 355): Not later than 120 days after the Secretary notifies the holder of an approved covered application that the Secretary has made a determination under subparagraph (A) with respect to the drug involved, or within such other reasonable time as the Secretary requires to protect the public health, the holder shall submit to the Secretary a proposed risk evaluation and mitigation strategy.

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I hereby take an oath that I wrote this master thesis independently and no other than the listed references were used.