

**An insight into the post-approval safety  
surveillance of medicinal products in the  
three ICH regions (EU, Japan and USA) -  
with particular focus on the management of  
safety signals**

Wissenschaftliche Prüfungsarbeit  
zur Erlangung des Titels

**„Master of Drug Regulatory Affairs“**

der Mathematisch-Naturwissenschaftlichen Fakultät  
der Rheinischen Friedrich-Wilhelms-Universität Bonn

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Bonn 2015

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## List of Abbreviations

ADR/ ADRs	Adverse Drug Reaction/ Adverse Drug Reactions
AERS	Adverse Event Reporting System ( <i>replaced by 'FAERS' in 2012</i> )
ASPEN	Asian Pharmacoepidemiology Network
CAT	Committee for Advanced Therapies
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures
COMP	Committee for Orphan Medicinal Products
CVMP	Committee for Veterinary Medicinal Products
CORDIS	Community Research and Development Information Service
DARRTS	FDA's Document Archiving, Reporting and Regulatory Tracking System
DEP	Division of Epidemiology
DHCP	Dear Healthcare Providers
DHPC	Direct Healthcare Professional Communication
DME	Designated Medical Event
DMEPA	Division of Medication Error Prevention and Analysis
DPV	Division of Pharmacovigilance
DRISK	Division of Risk Management
DSB	Drug Safety Oversight board
EC	European Commission
EMA	European Medicines Agency
EPITT	European Pharmacovigilance Issues Tracking Tool
EPPV	Early Post-Marketing Phase Vigilance

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EU	European Union
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDASIA	Food and Drug Administration Safety and Innovation Act
FD&C Act	Federal Food Drug & Cosmetic Act
GVP	Guidelines on Good Pharmacovigilance Practices
GPSP	Good Post-marketing Study Practice
HCPs	Healthcare Professionals
HMPC	Committee on Herbal Medicinal Products
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ( <i>short: International Conference on Harmonisation</i> )
ICSR/ ICSRs	Individual Case SafetyReport/ Individual Case SafetyReports
MAH/ MAHs	Marketing Authorisation Holder/ Marketing Authorisation Holders
MAPPs	CDER's Manual of Policies and Procedures
MHLW	Ministry of Health, Labour and Welfare
MHRA	Medicines and Healthcare Products Regulatory Agency
MIHARI	Medical Information for Risk Assessment Initiative
MP/ MPs	Medicinal Product/ Medicinal Products
NCA/NCAs	National Competent Authority/ National Competent Authorities
OPE	Office of Pharmacovigilance and Epidemiology
PAFSC	Pharmaceutical Affairs and Food Sanitation Council
PDCO	Paediatric Committee
PDUFA	Prescription Drug User Fee Act
PFSB	Pharmaceutical and Food Safety Bureau
PFSB/ELD	Pharmaceutical and Food Safety Bureau/ Evaluation and Licensing Division
PFSB/SD	Pharmaceutical and Food Safety Bureau/ Safety Division

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PIDM	WHO's Programme for International Drug Monitoring
PIL	Patient Information Leaflet
PMDA	Pharmaceuticals and Medical Devices Agency
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RA/ RAs	Regulatory Authority/ Regulatory Authorities
REMS	Approved Risk Evaluation and Mitigation Strategies
RMP/ RMPs	European Risk Management Plan/ Risk Management Plans
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SOPPs	CBERs Standard Operating Procedures and Policies
TME	Targeted Medical Event
UMC	Uppsala Monitoring Centre (a WHO Collaborating Centre)
UNESCO	United Nations Educational, Scientific and Cultural Organization
U.S. / USA	United States of America
USR	Urgent Safety Restriction
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organisation

## **Acknowledgements**

First I would like to thank Prof. Dr. Barbara Sickmüller and Dr. Axel Thiele for the supervision of this master thesis, for valuable suggestions and constructive feedback.

Thanks to the DGRA staff for the excellent organization of the MDRA study program. Barbara Röcher and Dr. Jasmin Fahnenstich merit special thanks for their continuous support.

Thanks to my company and my colleagues for the support and the opportunity to take many Fridays off to part at the MDRA study program.

Thanks to my family and friends for their marvellous support and for their patience.



## 1 Introduction

During the development of medicinal products (MPs) it is not possible to identify all potential safety concerns. Especially less frequent adverse drug reactions (ADRs) are unlikely to be observed during the clinical development, which is mainly due to the limited number of patients treated. For this reason post-authorisation safety surveillance is of paramount importance to ensure patient safety.

The essential tasks in post-authorisation safety surveillance are the identification of new or changing safety concerns and the subsequent, systematic evaluation followed by adequate action with regard to risk minimization activities. The detection of potential safety signals presents an early stage in the examination of possible safety concerns. Typically the need for further evaluation is justified, but it is not clear if a “real” risk with clinical relevance exists and if any regulatory action is warranted. The management of safety signals can be regarded as the basis of Pharmacovigilance (PV) activities and belongs to the most important performances of post-authorisation safety surveillance systems.

The European Union, Japan and the United States of America, the founding members of the International Conference on Harmonisation (ICH), have established pharmaceutical regulatory systems of the highest level worldwide. Their PV systems are not only based on long-standing experiences, but also on empirical knowledge gained from intensive international collaboration.

The present master thesis intends to provide an insight into the post-authorisation safety surveillance of MPs in the European Union, Japan and the United States of America, with focus on the management of safety signals. Beginning with a comprehensive overview on the core principles of signal management, the legal framework and the relevant organisational structures are described for each region respectively. It is explained how signal management processes are implemented into the national PV systems, taking into consideration the local requirements for ADR reporting as well as role and responsibilities of marketing authorisation holders (MAHs) and the competent regulatory authorities (RAs). As attention is increasingly turned to pre-emptive approaches, reference is also made to important projects and experiences in the area of proactive safety surveillance systems. With respect to international communication and cooperation, the WHO Programme for International Drug Monitoring is depicted. This master thesis is intended to provide not only an overview but also constitute a comparison of the signal management systems in the three ICH regions.

## 2 Key definitions and core principals

### 2.1 Definition of “signal”

Clear definitions in the field of PV are of considerable importance to ensure a universal understanding of safety issues and to enable systematic and reliable drug safety systems. However, in the field of PV, the term “signal” has been used a long time with ambiguity and without a clear, internationally adopted definition. (1) Back in 1992, the members of the World Health Organisation (WHO) Programme for International Drug Monitoring (PIDM) first agreed upon the use of harmonized definitions regarding regularly used terms in the area of PV. (2) The WHO defined a signal as:

*“reported information on a possible causal relationship between an adverse event and a drug, the relationship being previously unknown or incompletely documented. Usually more than a single case report is required to generate a signal, depending on the seriousness of the event and quality of the information“.* (2)

Over the years, in particular the diversity of sources providing new information about possible adverse reactions has evolved prodigiously, resulting in an enormous increase in information about the safety of MPs. (1) Therefore, after systematically examining and analysing the etymology as well as previous definitions, Hauben and Aronson propounded a new, more contemporary definition of the term ‘signal’ in a publication dated 2009. (3) Their accurate definition was soon utilized by CIOMS VIII and has been adopted by the experts with only slight modification in their final report of 2010. (1) The following definition presented by CIOMS VIII has become established and has achieved great international acceptance:

*“information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.”* (1)

The definitions above underline that a signal in terms of PV can be seen as an early indication that supports a suspicion on a potential causal relationship between a safety concern and a MP which needs to be further evaluated. The potential signal has a hypothetical character, as it is accompanied by uncertainty about the plausibility provided. Hence it is not to be treated like a confirmed risk, but must rather be handled in an accurate though individual way, depending in particular on its strength and its potential

harm. Signals are to be seen cautious in character, with subject to change depending on the outcome of the safety evaluation process.

### Utilization of the term “signal” in Europe

In Eudralex Volume 9A, the previous version of the official European PV guidance from 2008, the term “signal” was still used without a clear definition. (4) It was not until the publication of the particular module on signal management of the European Good Pharmacovigilance Practice (GVP) in 2012 (GVP-Module IX), that reference was being made to the CIOMS VIII definition mentioned above in an official document. (5)

### Utilization of the term “signal” in the USA

The provisions of the FDA currently do not particularly refer to the CIOMS VIII definition. Instead, the following definition for a “signal of a serious risk” is provided by the Federal Food, Drug and Cosmetic Act, 21 U.S. Code §355– 1(b):

*“The term “signal of a serious risk” means information related to a serious adverse drug experience associated with use of a drug and derived from—*

*(A) a clinical trial;*

*(B) adverse event reports;*

*(C) a postapproval study, including a study under section 355 (o)(3) of this title;*

*(D) peer-reviewed biomedical literature;*

*(E) data derived from the postmarket risk identification and analysis system under section 355 (k)(4) of this title; or*

*(F) other scientific data deemed appropriate by the Secretary.” (6)*

In the U.S. Pharmacovigilance guidance from 2005, “Guidance for Industry- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment”, a ‘safety signal’ is further described as:

*“a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified,*

*it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.” (7)*

### Utilization of the term “signal” in Japan

A short definition of the Japanese term for “signal” (シグナル) is found in a translation of the PFSSB/SD Notice: “Standard Operating Procedures for Medicinal Product Package Insert Revision”, dated February 10, 2010. (8) In part 2 (2) of the notice, signals are explained as „*adverse reactions that require attention*“. (8) Overall, the English term “signal” is rarely found in translated documents. In publications from the Ministry of Health, Labour and Welfare (MHLW) or in translations of the pharmaceutical laws and regulations provided by the Japan Pharmaceutical Manufacturers Association it is often spoken of ‘safety information’ in general. (9, 10)

## **2.2 Definition of “signal management”**

In addition to the sole definition of a safety signal, Module IX of the European Good Pharmacovigilance Practice (GVP) mainly speaks of the “signal management process” in general and defines this process in its introduction (part A) as:

*“the set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed. The signal management process shall include all steps from initial signal detection; through their validation and confirmation; analysis and prioritisation; and signal assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made”. (5)*

The signal management process is part of the risk assessment, because it aims to clarify if a safety finding represents an actual, identified risk (‘verified signal’), a potential risk (‘indeterminate signal’) or if it is “false positive” and therefore to be ruled out. (1) While ‘verified signals’ generally require risk management activities, e.g. labelling changes, changes in the marketing authorisation or even withdrawal of the authorisation, ‘indeterminate signals’ are usually continued to be monitored by routine PV activities. (1) However, in advanced steps of the signal management process it is decided whether any regulatory action is warranted and if so which measures for risk minimization and risk communication are necessary.

## 2.3 Description of a signal management process in general

The signal management steps outlined in the before mentioned definition correspond to article 21 (1) of the European Commission Implementing Regulation (EU) No 520/2012:

*“The signal management process shall include the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment, and recommendation for action.”*  
(11)

### Signal detection

There are different methods for the detection of safety signals, which can basically be divided in traditional methods and more complex statistical methods.

In former times the traditional PV systems started with manual clinical reviews and simple quantitative methods. The following table presents traditional signal detection methods as described by CIOMS VIII in their report of 2010.

<b>Traditional method</b>	<b>Description of safety signal generation</b>
“Index Case” / “Striking Case”	A well-documented case, with striking "striking" features.
Designated Medical Event (DME)	Typical adverse events, which are rare, serious and often caused by MPs (“e.g. aplastic anaemia, toxic epidermal necrolysis, Steven-Johnson syndrome, Torsade de pointes and hepatic failure”(1)).
Targeted Medical Event (TME)	Adverse events which are associated with a specific MPs or patient populations.
Hyper Acute Events/ “end-of-the-needle event”	Adverse events which are pharmacologically plausible and occur in a close temporal association with parenteral administration → always require special attention

Table 1: Traditional methods of signal detection: manual review of cases and case series according to CIOMS VIII. (1)

Traditional signal detection methods further include simple quantitative approaches, as e.g. the analysis of listings and/or cumulative overviews and the evaluation of reporting rates, frequencies or increases in the number of ADRs in a certain patient population. (1) Although more complex methods have been developed, traditional methods are still important because individual cases and case series can provide significant clinical input for the detection of signals, especially if the cases are well documented and of good

quality. (1) According to CIOMS VIII *“traditional methods [...] are, and in the foreseeable future will continue to be, a foundation of signal detection activities using spontaneous reports.”* (1)

The first more complex, statistical signal detection methods have been developed in the late 1990s, as complementary tools to screen large databases of spontaneous reporting systems and support traditional methods. (1) The complex statistical methods comprise a fast evolving range of computer-aided statistical approaches such as analyses of basic disproportionate reporting (comparison of relative reporting frequencies) and data mining algorithms. Several recognised methods are described in official guidelines (e.g. the ‘Guideline on the Use of statistical signal detection methods in the EudraVigilance data analysis system’ of 2008 (12) ) and in numerous publications (e.g. CIOMS VIII’s final report ‘Practical Aspects of Signal Detection in Pharmacovigilance’ of 2010 (1)).

It is important to underline that a general signal detection approach applicable for every safety issue is not possible and that the most suitable and most effective method has to be chosen situation specific instead. Article 20 of the Commission Implementing Regulation (EU) No 520/2012 states:

*“National competent authorities, marketing authorisation holders and the Agency [= EMA] shall determine the evidentiary value of a signal by using a recognised methodology taking into account the clinical relevance, quantitative strength of the association, the consistency of the data, the exposure–response relationship, the biological plausibility, experimental findings, possible analogies and the nature and quality of the data.”* (11)

### Signal validation/ confirmation

According to Article 20 of the Commission Implementing Regulation (EU) No 520/2012 GVP Module IX cites in part B.3.3.:

*“[...] ‘signal validation’ means the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.”* (11)

CIOMS VIII underlines that signal validation requires a thorough clinical and pharmacological knowledge including multi-disciplinary cooperation. (1) Depending on the source of information, CIOMS VIII describes several criteria for the evaluation (e.g. *“positive re-challenge(s) and/or de-challenge”*, *“known mechanism (including class effect) or biological plausibility”*, etc., when evaluating a case series). (1) CIOMS VIII points out that completeness and quality of the data are of paramount importance and

critical for an appropriate evaluation of a causal relationship between the safety issue and the medicinal product. (1)

### Signal Analysis and Prioritization

European GVP Module IX states in part B.3.4:

*“A key element of the signal management process is to promptly identify validated signals with important public health impact or that may significantly affect the benefit-risk profile of the medicinal product in treated patients. These signals require urgent attention and need to be prioritised for further management without delay.” (5)*

In signal management most attention should be focused on validated signals which justify a prompt, detailed and intensive processing. Strategies for the further assessment steps should be developed as early as possible. Important points to consider (e.g. the potential impact on patients, the clinical context or the novelty of the suspected adverse reaction) can be found in several official guidance documents as well as published literature, e.g. of CIOMS VIII. (1, 5)

### Signal Assessment

European GVP Module IX describes in part B.3.5:

*“The objective of signal assessment is to further evaluate a validated signal so as to identify the need for additional data collection or for any regulatory action. It consists of an assessment of the available pharmacological, non-clinical and clinical data and information from other sources.” (5)*

### Recommendation for Action

European GVP Module IX describes in part B.3.6:

*“Signal assessment results in a recommendation that either no further action is required at this point in time or a further action is needed. Although the recommendation for action normally takes place in logical sequence after signal assessment based on the extent of the information, the need for action should be considered throughout the signal management process.” (5)*

The initial action oftentimes includes the request for additional information and/ or additional investigations regarding the safety concern to be provided by the MAHs. Recommendations for action might further include regulatory risk minimisation actions as e.g. changes in the product information and labelling, the request to conduct further

clinical studies (e.g. post-authorisation safety studies) or in severe cases even emergency interventions as the suspension of the marketing authorisation of the MP.

Chapter 4-6 describe how signal management is conducted in Europe, the United States of America and Japan.

## 2.4 Important data sources for the detection of signals

The sources providing post-approval PV information for the detection of safety signals are diverse. (5) The ICH E2D Guideline 'Post-approval safety data management' from 2003 briefly describes a range of important sources and divides them into four different categories (13):

### 1) Unsolicited Sources

- Spontaneous reports (= individual case safety reports (ICSRs) reported by healthcare professionals or patients)
- Literature
- Internet
- Other sources (e.g. lay press, other media)

### 2) Solicited Sources

- Clinical trials
- Registries
- Patient use programs
- Patient support and disease management programs
- Surveys of patients or healthcare providers

### 3) Contractual Agreements

- Exchange of safety information between different companies

### 4) Regulatory Authority Sources

- National competent authorities
- Foreign competent authorities

Safety information is collected by various organisations, such as MAHs, manufacturers, wholesalers, regulatory authorities, drug-monitoring centres and also academic centres. (1) ICSRs are collected in organized data collection systems and the number of databases is immense. There are several national and international databases for the collection of general ADRs and even registries for the collection of specific types of ADR



(e.g. the registry for severe skin reactions<sup>1</sup> of the university hospital in Freiburg, Germany). (1) Some of the most important spontaneous reporting system databases with major relevance for the regions examined in this thesis are:

- EudraVigilance (EMA, European Union)
- ADR Information Management System (PMDA/ MHWL, Japan)
- FDA Adverse Event Reporting System 'FAERS' (FDA, USA)
- Vaccine Adverse Event Reporting System 'VAERS' (FDA, USA)
- Vigibase (Uppsala Monitoring Centre, WHO: see section 7.1)

A complete list is beyond the scope of this thesis, as there are numerous additional national databases (e.g. the yellow card database of the MHRA in the United Kingdom). For more detailed information in this area, reference is made to Appendix 3 of CIOMS VIII's 'Practical Aspects of Signal Detection in Pharmacovigilance' which provides a comprehensive overview including interesting characteristics of many important databases. (1)

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<sup>1</sup> Dokumentationszentrum schwerer Hautreaktionen (dZh)

## 2.5 CIOMS Working Group on Signal Detection

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization in the field of biomedical sciences. (14) It was founded in 1949 by the WHO and UNESCO and includes numerous members, e.g. regulatory authorities, pharmaceutical companies, and other institutions, which collaborate for the following aims:

- “ *To facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary;*
- *To maintain collaborative relations with the United Nations and its specialized agencies, in particular with WHO and UNESCO; and*
- *To serve the scientific interests of the international biomedical community in general.*” (14)

### CIOMS VIII: Application of Signal Detection in Pharmacovigilance (2006)

CIOMS has created several working groups addressing issues in the area of MP development and PV, including topics concerning post-authorisation safety surveillance of MPs in particular. (15) PV is an evolving science and the management of adverse drug reactions has changed tremendously in the past decades. CIOMS Working Group VIII was founded in 2006 to address those changes and “*establish a systematic and holistic strategy to better manage the entire “lifecycle” of a [safety] signal*”. (1)

In the following four years CIOMS VIII elaborated and developed points to consider in the general management of safety signals, in particular with regard to different approaches to signal detection and strategies to interpret signal assessment results. The final report of the working group is titled ‘Practical Aspects of Signal Detection in Pharmacovigilance’ and was published 2010. (1) It contains key definitions of PV, explains different signal detection methods (traditional, quantitative/statistical approaches), describes data sources including their challenges and limitations (e.g. ICSRs, databases) and points out various practical recommendations in strategic signal management aspects. (1) CIOMS VIII describes the signal management process as the “lifecycle” of a drug safety signal, including identification, prioritization and evaluation as the main steps. The general framework of the theoretical steps, as presented by CIOMS VIII, is depicted in figure 1 below. (1) However, the handling of safety signals is always situation specific and requires a high level of flexibility and CIOMS VIII emphasizes not to intend a presentation of recommendations on standard methods or strategies to be applied for all safety issues. (1)

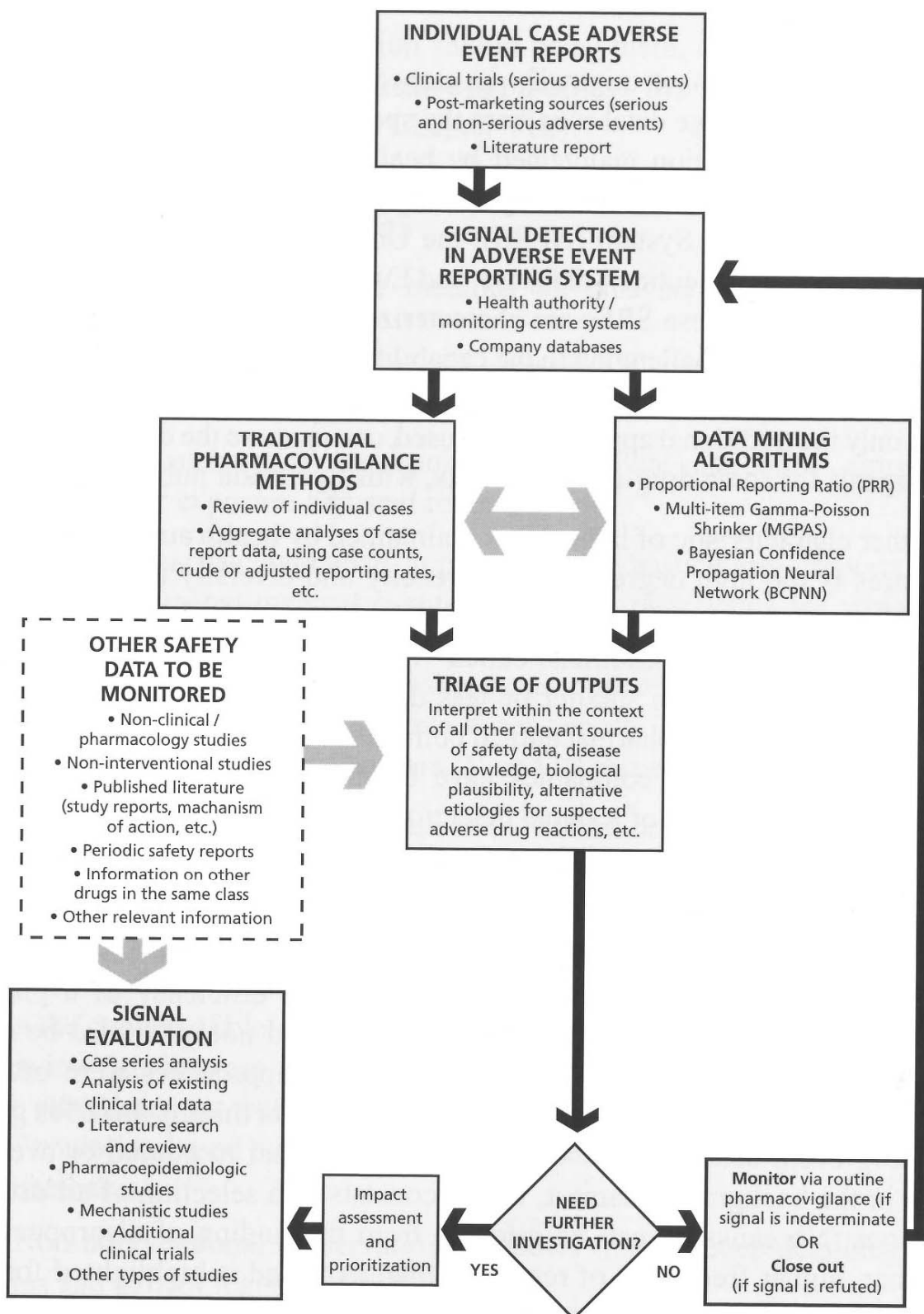


Figure 1: Signal Management Process according to CIOMS VIII Source: WHO, CIOMS VIII (1)

## 2.6 ICH - Aims of harmonization and differences in terminology

In times of globalisation, the safety of MPs has become an international responsibility and harmonised methodologies are advantageous to strengthen PV processing. The aim to harmonise PV systems on a global level is particularly driven by the founding members of the ‘International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use’ (ICH).

The initiative was founded in 1990 by regulatory authorities (RAs) and industry members of Europe, Japan and the USA. (16) The three pillars in the evaluation of medicinal products, “Safety, Quality and Efficacy”, were chosen as main topics for the elaboration of harmonised standards. (16) Throughout the years, several ICH working groups created guidelines which represent proposals to be implemented into the respective national legislations.

### ICH guidelines on PV

Code	Title
E2A	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
E2B (R3)	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E2C (R2)	Periodic Benefit-Risk Evaluation Report
E2D	Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting
E2E	Pharmacovigilance Planning
E2F	Development Safety Update Report

Table 2: ICH Guidelines on Pharmacovigilance (17)

The guidelines contain harmonised definitions as well as concepts and global standards, which in majority have been adopted by the national RAs of the three ICH regions either directly or modified as appropriate. The general PV systems in the ICH regions are therefore quite harmonized.

Nevertheless, in particular with respect to the terminology there are still some differences which become apparent after considering the common use of certain terms and expressions. For example:

- To describe the time before and after a marketing authorisation is granted, ICH uses the terms “pre- approval” and “post-approval” in its guidance documents (e.g. in E2D: Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting). (13) However, in Europe it is usually spoken of “post-authorisation” (e.g. in “post-authorisation safety studies”) and in the worldwide literature “post-marketing” is still a commonly used term (e.g. in “post-marketing requirements”, “post-marketing studies”). (10, 18, 19)
- In Europe a pharmaceutical medicine is named “medicinal product”, while in the translated Japanese documents and in the USA the common term is “drug”. To prevent irritation in this thesis, the term “medicinal product” is used regardless of the regions described.
- According to the definitions in ICH E2D “*an adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment*”. (13) An adverse reaction however is characterized by the suspicion of a causal relationship, a “*response to a medical product*” (13). While in Europe and Japan the post-approval reporting requirements are related to adverse reactions (10, 20), in the USA it is spoken of “adverse event reporting” in general (21). This might lead to the conclusion that in the USA every undesirable event of a person treated with a MP would pose an ICSR, even if not considered related to the MP. However, as spontaneously reported ICSRs usually result from a suspicion or at least an impression of the reporting person that there might exist a possibility of a causal relationship between the event and the MP, the term “adverse reaction reporting” seems more accurate for the use in post-approval PV and is therefore used in this thesis for all regions described to avoid confusion.

## 2.7 Historical development

The first PV systems have been developed during the 1960`s after the thalidomide tragedy, basically in form of initiatives encouraging spontaneous adverse reaction reporting. (1) PV systems have been steadily evolved ever since, as knowledge and understanding of safety concerns related with MPs have become more important. (1) In this context, in particular the past decades are characterised by significant progresses. Post-authorisation safety surveillance systems and signal management activities have been expanded and improved in many countries worldwide.

Early systems involved mainly paper-based safety reporting followed by manual review of individual cases or case series and included simple quantitative methods for signal detection. (1) Safety monitoring was performed in a rather passive way, supported by the classic review of spontaneous reporting systems for the most part. (1)

Today, modern PV systems include rapid electronic reporting and standardized message and are becoming more and more transparent to the public. The existents of a variety of different ADR databases worldwide with quickly growing datasets has further set up the way for improved quantitative approaches in the detection of safety signals. Advanced quantitative techniques (e.g. statistical or mathematical tools, keyword: ‘data mining’) are developed to enhance the data quality and facilitate the identification of safety signals in a more pre-emptive and proactive way.

Despite all progress, the task to find appropriate ways of performing efficient signal detection is often challenging. The generation of safety signals and all further steps should ideally be systematic on the one hand and sufficiently individual on the other side, because the handling of all safety signals requires a careful consideration of the specific situation, in particular taking into account possible local requests.

## **2.8 Quality and documentation**

Overall, for the interpretation of safety data from spontaneous reporting it is highly important to keep in mind possible limitations and biases, e.g. reporting biases. There are numerous factors which can affect the degree of reliance of information from all kind of data sources. In particular incomplete ICSRs, duplicates, under- and overreporting, stimulated reporting or the lack of causal clarity and missing information are common challenges. (1) The quality of signal detection activities and further signal management steps relies to a high extend on the quality of the safety information provided.

Further, the generation of safety signals is a permanent and ongoing process in the life-cycle of MPs. Continuous safety surveillance is essential for a regular evaluation of the benefit-risk profile. In regions as the EU, Japan and the USA, where PV activities are regulatory required and well established, the key processes are expected to be properly documented and quality controlled. (7, 10, 22) Important post-authorisation safety practices must be reflected in standard operating procedures (SOPs) and appropriately qualified personnel is regarded as indispensable to operate a good signal management system and ensure high quality safety profiles of the MPs. (1) Internal inspections and controlling measures of routine PV tasks are expected compliance management tools, though PV inspections are usually also conducted by RAs. (22) The individual provisions and requirements relevant for the management of safety signals in post-approval PV are explained below for each of the three ICH-regions.

## 3 Regulatory framework

### 3.1 Legal framework

#### 3.1.1 Relevant provisions in the European Union

##### Legislation

In the European Union (EU), the laws for the regulation of MPs marketed in the EU are developed by the European Commission (EC) and adopted by the European Parliament and the Council of the European Union. (23) The legal basis for PV provisions is provided by Title IX Articles 101-108 of Directive 2001/83/EC for nationally authorised products and Title II Chapter 3 Articles 21-29 of Regulation (EC) No 726/2004 for centrally authorised products respectively. (20, 24) Signal management is a key process for compliance with the EU legislation and a PV system including signal detection as well as the continuous monitoring and evaluation of the risk-benefit profile of MPs is required by the aforementioned laws. (20, 24)

Over the past years, the PV requirements in the EU have been progressively developed to increase the vigilance of the system and to ensure a high level of public health protection. Particularly under the “new EU Pharmacovigilance legislation”<sup>2</sup>, which was adopted in 2010 and came into effect in 2012, important legal provisions were implemented amending Directive 2001/83/EC and Regulation (EC) No. 726/2004 and introducing major changes. (25, 26) PV requirements were strengthened in general, aiming to “*reduce the number of ADRs in the EU*” (27) by the implementation of higher standards regarding the protection of public health. One important key element was the improvement of the European system for the collection and monitoring of suspected adverse drug reactions to detect possible safety signals more quickly and efficiently. (11) To maintain a high level of expertise in the assessment of safety issues, a new scientific committee was established: the Pharmacovigilance Risk Assessment Committee (PRAC). (11)

In the Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012, operational details with regard to significant aspects related to the performance of PV activities are further specified. (11) Details concerning the handling of safety signals are found in chapter III, Articles 18-24 of the Commission Implementing Regulation: “Minimum requirements for the monitoring of data in the EudraVigilance database” (11):

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<sup>2</sup> Regulation (EC) No 1235/ 2010, Directive 2010/84/EU

- Article 18: General requirements
- Article 19: Identification of changed risks and new risks
- Article 20: Methodology for determining the evidentiary value of a signal
- Article 21: Signal management process
- Article 22: Worksharing for signal management
- Article 23: Signal detection support
- Article 24: Signal detection audit trail.

### Guidelines

The legal instruments mentioned above are further supported by various guidelines. Of particular importance is the “Guideline on Good Pharmacovigilance Practices” (GVP), which is addressed to all stakeholders involved in PV. (28)

Being coincident with the latest legislation, GVP has been issued by the European Medicines Agency (EMA) to replace Eudralex Volume 9A “The rules governing MPs in the European Union - Pharmacovigilance” and to facilitate accomplishing the broad tasks of PV. (28) With several hundred pages the European GVP is already extremely comprehensive, although some parts are still under development. Divided into 15 different modules covering the most important PV processes, GVP is to be completed by additional chapters on product- or population-specific considerations and annexes. (28)

GVP module IX “Signal Management” is entirely dedicated to the lifecycle of safety signals in particular. It is in effect since July 2012 and was created „*to provide general guidance and requirements on structures and processes involved in signal management [and] to describe how these structures and processes are applied in the setting of the EU Pharmacovigilance and regulatory network*”. (5) Module IX comprises the following three sections (5):

- A. Introduction including the definitions of signal and signal management.
- B. General requirements on structures and main processes. This section includes information and guidance with regard to the data sources and different methods of signal detection, a description of the six steps of a signal management process and overall quality aspects.
- C. Description of the function of the EU PV network with clear definitions of the responsibilities and tasks of all parties involved (MAHs, NCAs, EMA and PRAC).

Specific recommendation and practical considerations with regard to the performance of statistical signal detection are given by the “Guideline on the use of statistical signal-detection methods in the EudraVigilance data analysis system” (12). It was published in 2008 and explains in particular:



*“quantitative methods implemented in the EudraVigilance Data Analysis System together with the elements for their interpretation and their potential limitations in the frame of Pharmacovigilance. It encompasses the use of quantitative methods in EudraVigilance applied to the evaluation of ICSR’s originating from health care professionals and involving authorised medicinal products”.* (12)

The following GVP Modules also deserve to be mentioned in context of provisions concerning signal management:

- GVP Module I – “Pharmacovigilance systems and their quality systems” depicts the core principles and expectations on PV systems including structures and the main processes. (22) Further, overall quality and responsibilities are defined. (22) With regard to critical PV processes, continuous monitoring of the drug related risk-benefit profile and signal management are mentioned in particular. (22)
- Module V – „Risk management systems” depicts the core principles of an effective risk management system. (29) It provides guidance regarding the structure and format of an adequate risk management plan and gives recommendations for risk minimisation measures. (29) Risk management systems aim to identify possible risks as early as possible to set up appropriate countermeasures if considered necessary, always with regard to individual the risk-benefit profile. Signal detection plays an important role in the identification and generation of new or changed risks. (29) Accordingly there is a close association between signal management activities and risk management.
- Module VI – “Management and reporting of adverse reactions to medicinal products” gives wide-ranging recommendations on *“the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products”* (30) and on the reporting of emerging safety issues, which might also arise from signal detection activities. (30) The module is further essential with respect to signal detection, because individual case safety reports (ICSRs) provide an important data source for safety information.
- Module VII – “Periodic safety update report (PSUR)” provides guidance *“on the preparation, submission and assessment of PSURs”*. (31) In a PSUR all available information that might have an impact on the risk-benefit profile of the MP is described, including data on benefit and/or harm. (31) The information is pre-

sented in a predetermined format and critically examined and evaluated. (31) With particular concern to the presentation of safety signals that were generated, evaluated or closed during the reporting period, section 15 “Overview of signals: new, ongoing, or closed” was set. (31) PSUR section 16 “Signal and risk evaluation” further provides information on “*the subsequent classification of these signals and the conclusions of the evaluation*“. (31)

### 3.1.2 Relevant provisions in the United States of America

#### Legislation

The regulatory requirements of the United States Food and Drug Administration (FDA) are published under Title 21 Code of Federal Regulations (CFR). (6) Chapter 9 of the ‘U.S. Code: Title 21 – Food and Drugs’ is dedicated to the Federal Food Drug & Cosmetic Act (FD&C Act). (21) Relevant provisions with regard to PV, especially those concerning safety reporting requirements, are mainly found in 21 CFR Part 312 for investigational new drug applications, in 21 CFR Part 314 for new drug applications, in 21 CFR Part 600 for biologics, in 21 CFR Part 1271 for cellular and tissue based products and in Section 760 of the FD&C Act for non-prescription drugs. (6, 21)

In the past decade, two important amendments to the FD&C Act included significant impacts in the field of Pharmacovigilance (32):

- 2007: the Food and Drug Administration Amendments Act (FDAAA) and
- 2012: the Food and Drug Administration Safety and Innovation Act (FDASIA).

#### FDAAA (signed into law in 2007)

In addition to the fourth reauthorisation and expansion of the Prescription Drug User Fee Act (PDUFA), which broadened FDA’s drug safety program, the FDAAA contained important amendments with regard to PV by providing Title IX “Enhanced Authorities Regarding Postmarket Safety of Drugs”. (33) Amongst others, the FDAAA gave the FDA an increased authority concerning post-authorisation safety surveillance. (33) Under section 901 the agency is authorized to order labelling changes due to new safety information, may require additional studies or clinical trials under certain circumstances and is in the position to impose civil monetary penalties for certain violations of the FD&C Act. (33) According to section 505 (k) (5) of the FD&C Act (21 U.S.C. 355), which was introduced by Title IX, Section 921 of the FDAAA of 2007<sup>3</sup>, the FDA is required to:

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<sup>3</sup> see pg 121 stat. 962 of U.S. FDAAA of 2007 (33)

*“conduct regular, bi-weekly screening of the Adverse Event Reporting System database [FAERS] and post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by Adverse Event Reporting System within the last quarter.” (33)*

Thus the Agency is obliged to perform signal detection on a regular basis and to inform the public about all significant findings. By FDAAA the FDA was ensured additional personal resources in order to manage all further tasks of its mission to advance public health. (33)

#### FDASIA (signed into law in 2012)

FDASIA contained the fifth reauthorisation of the PDUFA, which further expanded FDA’s authority to strengthen its ability to safeguard and promote public health. (34) In addition the FDA published a list of performance goals and procedures for PDUFA V, “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013-2017”. (35) The PDUFA V commitments encompass several goals pertaining to PV and concerning the enhancement and modernisation of the safety of MPs in the USA:

- Measurement of the effectiveness of risk evaluation and mitigation strategies (REMS) and development of ways to standardize and integrate those REMS into the evolving healthcare system. (35)
- The enhanced, determinate use of “Sentinel” as a tool for evaluating drug safety signals, focussing on safety issues of class effects that affect multiple products. (35)
- The modernisation of certain processes in the field of PV, in particular with regard to the development of an appropriate information technology infrastructure, which aims to maximise the efficacy of tools used for adverse event signal detection and risk assessment. (35)
- An improvement of the drug information systems, including the adverse event reporting system (AERS), surveillance tools and the IT- infrastructure. (35)

#### Guidance

In addition to the regulations and laws mentioned above, the FDA also provides several forms of supportive, nonbinding guidance documents. According to the FDA, Guidance documents stand for the FDA’s current view on an issue and:

*“[... ] do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used*

*if such approach satisfies the requirements of the applicable statute, regulations, or both.” (36)*

The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) further give procedural recommendations in form of “Manuals of Policies and Procedures” (MAPPs) or “Manuals of Regulatory Standard Operating Procedures and Policies” (SOPPs) respectively.

According to the PDUFA III commitments of 2002, FDA has developed three important guidance documents for industry on the following risk management practices for medicinal products (7):

- Premarketing Risk Assessment (‘Pre-marketing Guidance’)
- Development and Use of Risk Minimisation Action Plans (‘RiskMAP Guidance’)
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (‘Pharmacovigilance Guidance’)

The final guidance documents have been published in 2005 and are still valid in 2015. The key document with regard to post-marketing PV is the ‘Guidance for Industry-Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment’, also called ‘Pharmacovigilance Guidance’. It was developed by the PDUFA III Pharmacovigilance Working Group (a group of experts of CDER and CBER) and outlines the role of post-authorisation safety surveillance in terms of risk assessment and risk minimization. (7) The Guidance in particular gives practical recommendations to industry on processes regarding “(1) safety signal identification, (2) pharmacoepidemiologic assessment and safety signal interpretation, and (3) pharmacovigilance plan development” (7), activities which correspond to the description of a signal management process in the area of PV.

The FDA also published several other guidance documents with relevance for signal management:

- The “Guidance Drug Safety Information - FDA’s Communication to the Public” of 2007 outlines how the FDA makes important safety information regarding MPs, including emerging drug safety information, available to the public. (37) A revision is currently under development; a draft of the updated version was first published in March 2012. (37)
- The “Guidance for Industry and FDA Staff - Dear Health Care Provider [DHPC] Letters: Improving Communication of Important Safety Information”

of 2014 describes the communication of safety updates on MPs to HCPs via Dear Health Care Provider (DHCP) letters. (38)

- MAPP 6700.9 “FDA Posting of Potential Signals of Serious Risks Identified by the Adverse Event Reporting System” (39) and SOPP 8420 “FDAAA Section 921: Posting of Potential Signals of Serious Risk” (40) from 2011: describe the policy and general procedures for the development and publication of “*quarterly lists of potential signals of serious risks identified by the Adverse Event Reporting System (AERS) in response to the Food and Drug Administration Amendments Act of 2007 (FDAAA).*” (40)
- MAPP 4121.2<sup>4</sup> “Tracking of Significant Safety issues in Marketed Drugs - Use of the DARRTS Tracked Safety Issues” explains how FDA staff works with the Document Archiving, Reporting, and Regulatory Tracking System (DAARTS). (41)
- Draft Guidance “Classifying Significant Postmarketing Drug Safety Issues” (2012): describes the process that the FDA intends to use for prioritization of significant safety signals and to classify adverse drug events as “*priority, standard, or emergency*”. (18)

### 3.1.3 Relevant provisions in Japan

#### Legislation

The legal basis for PV provisions related to MPs marketed in Japan is set by the “Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices” (Abbreviated: Pharmaceutical and Medical Devices Law), formerly called “Pharmaceutical Affairs Law”. (9) By MHLW act No. 84 in 2013, the title was revised as part of the ‘Law for Partial Revision of the Pharmaceutical Affairs Law’, which was implemented in November 2014 and among others included amendments to further strengthen post-authorisation safety surveillance of MPs (e.g. by the introduction of the ‘Package Insert Notification System’). (9, 42)

The Japanese PV requirements include a comprehensive reporting system for ADRs related to post-authorisation safety surveillance of MPs, as outlined in Articles 68/10 (§§1, 2), 68/13 (§3) and 68/24 Pharmaceutical and Medical Devices Law and Article 228/20 of the Enforcement Regulations of the Pharmaceutical and Medical Device Act.

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<sup>4</sup> In the first revision of 2011, the guidance of 2009 was renumbered from 6700.4 to 4121.2 (41)

(43) The regulation obliges not only MAHs, but also all medical institutions (clinics, hospitals, pharmacies, etc.) and HCPs (physicians, pharmacists, dentists, etc.) to collect safety information and report to the Pharmaceuticals and Medical Devices Agency (PMDA), the national competent authority in Japan, for information processing. (9, 43) By Article 68/13, §3 Pharmaceutical and Medical Devices Law, the PMDA is stipulated to analyse and evaluate the safety information received and hereby perform signal management activities. (43)

### Ordinances and Notifications

For the proper implementation and enforcement of legally binding regulations, the MHLW issues administrative ordinances. For additional guidance, notices and notifications are published whenever considered necessary.

The Japanese pharmaceutical regulation provides two important ordinances with reference to PV and significance for signal management in Japan: the MHLW Ministerial Ordinance No.135 of 2004, called ‘Ordinance on Good Vigilance Practices’ (GVP Ordinance) and the MHLW Ordinance No. 171 of 2004, called ‘Good Post-marketing Study Practice’ (GPSP).

The GVP Ordinance comprises the main principles of safety management in post-authorisation PV, as defined in the Pharmaceutical and Medical Devices Law. (10) In March 2013, the document has been amended by the PFSB Notification No. 0311/7 to enforce MHLW Ordinance No. 26 and include enhanced guidance on risk management plans. (43) The Japanese GVP currently comprises the following articles (10):

1. Purpose
2. Definitions of terms
3. Duties of general marketing compliance officer
4. Organizations and personnel involved in safety assurance
5. Standard operating procedures for post-marketing surveillance
6. Duties of the safety management supervisor
7. Collection of safety management information
8. Drafting of safety assurance measures based on examination of safety management information and the results thereof
9. Implementation of safety assurance measures and Risk management plan (RMP)
10. Early post-marketing phase vigilance
11. In-house inspections
12. Education and training
13. Standards for post-marketing safety management of MAHs of drugs other than prescription drugs and controlled medical devices

14. Standard for post-marketing safety management of MAHs of quasi-drugs, cosmetics and ordinary medical devices
15. Retention of records related to safety assurance

Articles 7-9 of the GVP Ordinance are of particular significance with regard to signal management activities. According to article 7 it is mandatory for MAHs to collect safety information from various sources, including e.g. HCPs, scientific meetings, literature screenings or national and international governmental institutions/ organisations. (10, 44) Articles 8 and 9 of the GVP Ordinance specify provisions with respect to the demand for an evaluation of this safety information, as well as the appropriate documentation and further measures to precede regarding safety assurance and possible implementation in RMPs. (10)

Further, article 5 of the GVP ordinance clearly demands various SOPs concerning the most important post-marketing safety surveillance measures. (10) It is expected that all important processes, e.g. the collection of safety information or the drafting and implementation of safety assurance measures, are internally reported in writing and that records of those reports are properly recorded. (10) Article 11 lays down the requirements regarding internal inspections with respect to activities concerning the safety management in pharmaceutical companies and article 12 sets out the requirements regarding appropriately qualified personal.

Good Postmarketing Study Practices (GPSP) however specifies respective rules related to different kinds of post-marketing surveys, which are mainly conducted for re-examination and re-evaluation purposes. Especially “drug use-result surveys” and clinical trials performed in order to gain additional data and information on quality, safety and efficacy are handled in the GPSP guidance document. (10) The GPSP has also been amended in March 2013 by the provisions mentioned above to include enhanced guidance on risk management plans. (43)

A selection of additional notices with relevance regarding the handling of safety signals is shown below. The Ministry notifications are frequently revised and published under new notification numbers, the following list presents notifications of currently valid guidance documents:

- PFSB Notification No.1002/20 of 2014 provides advice on the handling of adverse drug reaction reports (ADRs) and includes definitions, reporting deadlines, reporting forms and the address for submission of reports. (45)

- PFSB Notification No. 0325/19 of March 2015 presents the latest revision of the standard operating procedures for the Japanese safety information reporting system. The SOP includes information on reporting conditions, methods, forms, and timeframes concerning the proper reporting of ADRs, Infections and defects and briefly informs about the further procession of the reported information by the CA. (43)
- The Notice of PFSB/ELD and PFSB/SD dated February 2014 is a Q&A document about the reporting of ADRs and other relevant safety data gained during the post-marketing phase. (46)
- PFSB/SD Notice of February 10, 2010 is titled “Standard Operating Procedures for Medicinal Product Package Insert Revision“ and describes the collection and screening of reported safety data by the PMDA and subsequent measures regarding a revision of package leaflets. (8, 43)
- With notification PFSB/SD No. 1031/1 of 2014, a guideline handling the provisions regarding emerging safety information was issued. The document gives advice about the criteria for preparation of urgent safety information and describes methods and handling of the activities regarding the communication to HCPs and public in detail. (43, 47)

## 3.2 Regulatory structures

### 3.2.1 Organisation and responsibilities in the European Union

The EU holds a European medicines network, which is in charge of the general protection of public health by handling regulatory affairs related to MPs marketed in the EU. (23) The network comprises the EC, the European Parliament, all national competent authorities, the European Medicines Agency (EMA), and several other decentralised agencies. (23) PV activities are further conducted “*in close cooperation with healthcare professionals and the pharmaceutical companies themselves*”. (48) The EMA can be regarded as the centre of the European network and is located in London. (23) The EMA is not only responsible for the evaluation and supervision of marketing authorisations of certain MPs on the European market, but also for the establishment and maintenance of a European PV system throughout the EU-wide network. (23)

The EMA holds several divisions and departments supervising the Agencies core functions, including the Inspections & Human Medicines Pharmacovigilance Division with the Pharmacovigilance Department. (49, 50) The Pharmacovigilance Department is divided into two areas: Signal Management and Monitoring & Incident Management and



works in collaboration with the European network as well as with international partners, e.g. the World Health Organization (WHO) and regulatory authorities of countries outside the European Union. (23, 50)

The scientific assessment at the EMA is mainly performed by the following committees, who are in charge of the main functions of the Agency (51):

- Committee for Medicinal Products for Human Use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for Orphan Medicinal Products (COMP)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee on Herbal Medicinal Products (HMPC)
- Committee for Advanced Therapies (CAT)
- Paediatric Committee (PDCO).

In the interest of a further increase of transparency and better communication on PV issues, highlights, agendas and minutes of the committee meetings are published on the EMA-website on a regular basis. Due to their involvement in the signal management process, CHMP, PRAC, as well as the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) will be briefly portrayed below.

- Committee for Medicinal Products for Human Use (CHMP)  
The CHMP performs scientific assessments and prepares the official opinion of the EMA, mainly but not limited to centrally authorised MPs. (48) With regard to PV, the CHMP is also in charge of an ADR-monitoring and may recommend modifications, including ‘urgent safety restrictions’ (USR), or even the suspension or marketing-withdrawal of valid marketing authorisations to the EC. (48)
- Pharmacovigilance Risk Assessment Committee (PRAC)  
The PRAC meets monthly for four days and holds the key functions in the field of PV. PRAC thoroughly evaluates and monitors various aspects related to safety issues and risk management of MPs in the EU in order to provide scientific recommendations to CHMP and CMDh. (51, 52) One of the core topics of every PRAC meeting is the discussion of safety signals. Based on the requirements provided by GVP IX, PRAC holds responsibility for prioritization, analysis and assessment of validated and confirmed safety signals. Depending of the type of marketing authorisation, PRAC delivers recommendations to the CHMP (for centrally authorised MPs) or the CMDh and/or Member States (for nationally authorised MPs) respectively. The PRAC is composed of qualified members with high expertise in the field of PV, including independent scientific experts as well as one representative each for HCPs and patient organisations resp. (52)

- Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh)

The CMDh owns the mandate for the examination of questions which apply to marketing authorisations of MPs authorised via the mutual recognition or decentralised procedure, including the corresponding PV activities. The CMDh supports Member States when there appears to be a lack of consensus regarding potential safety issues during assessments and tries to reach a joint agreement to avoid arbitration procedures at the competent EMA committee (e.g. the CHMPC). (53) In order to present an official CMDh positions within a European PV assessment procedure (referral), the CMDh is supported by the PRAC and its recommendation. (53)

The NCAs of the European Member States work in close cooperation and have developed worksharing procedures in order to avoid duplication of work and to reach common decisions. This also applies to PV activities and assessments performed due to safety related issues. The legal basis for worksharing in the field of signal management activities is given in article 22 of the Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012. (11)

### **3.2.2 Organisation and responsibilities in the United States of America**

In the United States of America (USA), the Food and Drug Agency (FDA) is in charge of pharmaceutical regulatory affairs. The FDA is a large federal agency belonging to the United States Department of Health and Human Services and consisting of several offices and centres. The Office of Medical Products and Tobacco includes the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), who are responsible for scientific reviews with regard to quality, efficacy and safety of MPs and biologics respectively. (54)

CDER and CBER likewise hold various offices, divisions and subdivisions. Of special importance with regard to PV is the CDER Office of Surveillance and Epidemiology (OSE). The OSE is in charge of review and evaluation of safety related issues during the complete lifecycle of a MP and holds key functions in post-authorisation safety surveillance. (55) As shown in the organisational chart below, the OSE is divided into two offices and holds six divisions managing the core functions:

- the Office of Pharmacovigilance and Epidemiology (OPE) with the Divisions of Pharmacovigilance (DPV I & II) and Epidemiology (DEP I & II) and
- the Office of Medication Error Prevention and Risk Management with the Divisions of Medication Error Prevention and Analysis (DMEPA) and Risk Management (DRISK). (56, 57)

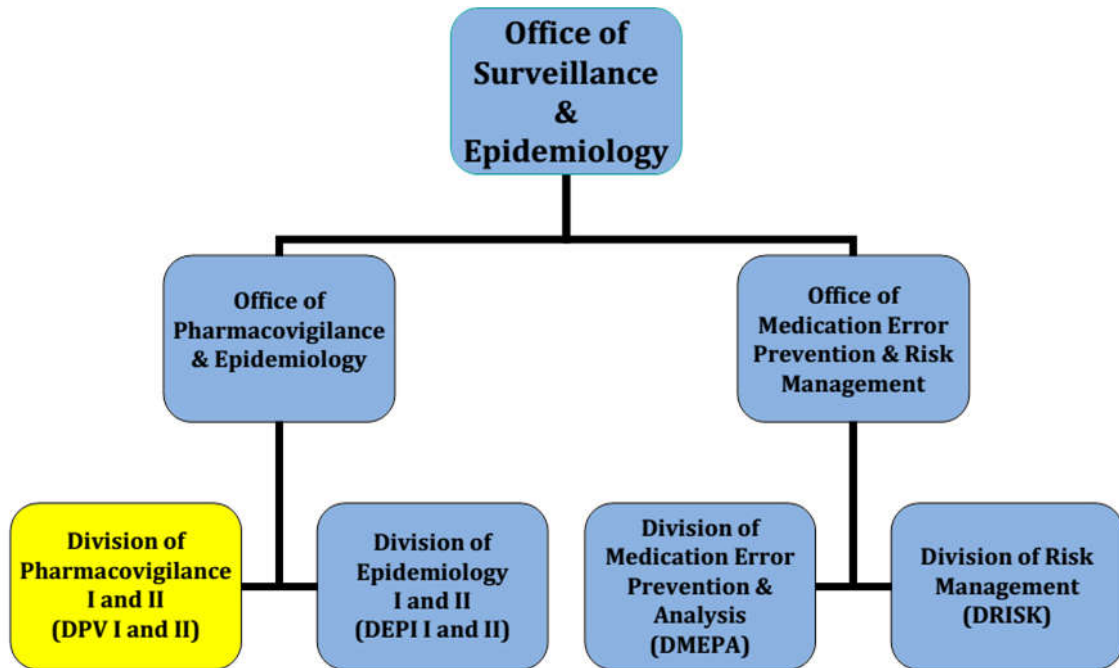


Figure 2: Organizational Chart of the FDA Office of Surveillance and Epidemiology (OSE). Signal management activities are mainly performed by the Division of Pharmacovigilance I and II (*in yellow*). Source: FDA (57)

The Drug Safety and Risk Management Advisory Committee is one of currently 33 advisory committees of the FDA. (58) The Committee mainly consists of scientific and medical experts (as well as one “*qualified member [...] identified with consumer interests*” and optionally “*one non-voting member who is identified with industry interests*” (59)), who meet on a regular basis to discuss relevant matters in the field of risk management and risk communication. In their meetings they further perform evaluations and provide recommendations on current safety-related issues, including possible safety signals. (59)

The CDER further holds an advisory group, the Drug Safety Oversight board (DSB), which in particular assists the Center with regard to the “*handling and communication of important and often emerging drug safety issues*” (60). The DSB exists since 2005, was stipulated by the FDAAA in 2007, and consists of numerous members belonging to different wide-ranging governmental, healthcare-related organisations who meet monthly to discuss urgent safety matters together. (60) According to the FDA, this has the advantage that various different points of view can be regarded and taken into account, before a final decision on urgent safety issues is made. (60)

### 3.2.3 Organisation and responsibilities in Japan

#### Ministry of Health, Labour and Welfare

In Japan, the Ministry of Health, Labour and Welfare (MHLW) is in charge of the general health care system. The MHLW consists of several bureaus and departments and also includes various councils, affiliated institutions as well as local and external bureaus. (61, 62)

The Pharmaceutical and Food Safety Bureau (PFSB) is a core part of the ministry and presents the governmental authority responsible for pharmaceutical regulatory affairs. The PFSB consists of the Department of Food Safety and the following five divisions (61):

- General Affairs Division (incl. Office of Drug Induced Damages)
- Evaluation and Licensing Division (incl. Office of Medical Devices Evaluation and Office of Chemical Safety)
- Safety Division
- Compliance and Narcotics Division
- Blood and Blood Products Division

The PFSB holds key functions with regard to the supervision and assurance of efficacy and safety of MPs on the Japanese market. (61) The PFSB develops policies and SOPs which help to establish recent provisions and are made public in form of notifications or notices. (61)

The Health Policy Bureau also belongs to the ministry proper. Its Economic Affairs Division is responsible for various policies related e.g. to manufacturing, marketing, distribution and trade of pharmaceutical products, while the research and development division among others is in charge of “*matters related to the improvement of health care information-processing and management system*”. (61)

The Pharmaceutical Affairs and Food Sanitation Council (PAFSC) presents the scientific advisory body of the MHLW. The council consists of two departments, the Pharmaceutical Affairs Department and the Food Sanitation Department. Several committees of scientific experts meet on a regular basis to review, evaluate and debate relevant matters, as e.g. the approval of medicines, re-evaluations or other important issues. (61)

#### Pharmaceuticals and Medical Devices Agency

The Pharmaceuticals and Medical Devices Agency (PMDA) was established after a comprehensive governmental reorganisation in 2004. (61) It represents a large, independent administrative organisation which operates in close cooperation with the MHLW. (61) PMDA is responsible for a major part of the operational regulatory work

and prepares recommendations for the MHLW. (61, 63) The three major tasks related to risk management activities are:

- scientific evaluations in form of various regulatory reviews,
- monitoring of post-marketing safety and
- relief services for persons suffering health injuries from ADRs or infections caused by MPs . (61, 63)

### PMDA's "Safety Triangle"



Figure 3: The "Safety Triangle" depicts the three key functions of the PMDA: Review, Safety and Relief. Source: PMDA (63)

The PMDA safety measures for risk mitigation comprise in detail:

- *"Collection, analysis, and dissemination of information related to the quality, efficacy, and safety of drugs and medical devices"*
- *Consultations with consumers and other parties concerning drugs and medical devices*
- *Guidance and advice for manufacturers, etc. to improve the safety of drugs and medical devices" (61)*

Post-approval safety surveillance activities performed or monitored by the PMDA also include the evaluation of clinical trials, "Early Postmarketing Phase Vigilance" (EPPV), which is a concentrated proactive surveillance system during the first 6 month of marketing of new MPs, as well as re-examinations of authorised MPS after a certain period of time (depending on the type of MP). (43) PMDA plays an important role in the Japanese PV system and is the responsible RA for signal detection and further signal management activities in Japan. (63) However, PMDA is only authorized to prepare scientific opinions and recommendations for the MHLW. (61) Decisions for action are made by the MHLW. (43, 61)

Finally, with respect to the structure it is to mention that PMDA is divided into the Review Department, the Safety Department and the Relief Department and altogether holds more than 20 offices. In the past years the number of employees has constantly increased, from 2009-2014 by almost 45%. (63) Thereof the Safety Department has almost doubled its capacities and in 2014 employed around 20 % of the total PMDA staff. (63) The Safety department includes the Chief Safety Officer, Offices of Safety I and II, Office of Manufacturing/ Quality and Compliance and the Inspection Division (“Kansai Branch”). (61, 63) The numbers are quite impressive and demonstrate the exceedingly increased governmental awareness for PV of MPs. The table in Annex A shows more detailed information about the number of PMDA employees from April 2009- April 2014.

## 4 Signal management in the European Union

### 4.1.1 Reporting requirements of ICSRs

Provisions with regard to the management of suspected adverse drug reactions are found in Title IX, Chapter III of Directive 2001/83/EC ('Recording, reporting and assessment of pharmacovigilance data'). (20) With Articles 107 (1) and 107a (1) of Directive 2001/83/EC, the European legislation requires adequate systems for the collection and recording of reported suspected adverse reactions on the level of NCAs and MAHs.

In course of the new PV legislation HCPs and consumers are increasingly encouraged to report suspected ADRs. This is done in particular by the implementation of a note in SmPC and PIL with the particular contact details of the NCA in charge and by supporting several reporting facilitations as e.g. the development of national web-portals for ADR-reporting. (20)

As described in chapter 3 of this thesis, GVP Module VI provides detailed information on the handling of adverse drug reactions and the reporting requirements. Electronic reporting of individual case safety reports (ICSRs) in a standardized format (E2B in xml file) is mandatory since 2005. (12) In the future, adverse reaction data of all 28 European member states shall be centralised in one single database, the EudraVigilance portal. (25)

Provisions regarding the time-frames for reporting are provided in Article 28 (1) of Regulation (EC) No 726/2004 and Article 107(3) and 107a(4) respectively. In general, irrespective of the expectedness, ICSRs containing serious suspected ADRs must be reported within 15 days from the date of receipt of the information. ICSRs containing non-serious suspected ADRs generally are to be reported by the MAH within 90 days. The development of the EudraVigilance system is currently not completed yet. Therefore transitional provisions provided in Article 2(4), 2(5) and 2(6) of Directive 2010/84/EU are in effect. (25) The time-frames for reporting of ICSRs during the interim-period and thereafter are briefly outlined below (see table 3). As soon as the development of the EudraVigilance database is completed, ADR reporting shall always be addressed directly to the EudraVigilance portal. (25, 30) This aims to facilitate reporting practices and shall ensure a direct transfer to the central EU ADR database without any delay.

In addition to the requirement of reporting spontaneous ICSRs, MAHs are also obliged to report suspected ADRs received from literature monitoring activities. However, in July 2015 the EMA has started a literature monitoring service and screens a defined list of published literature itself. To avoid duplicates, MAHs must only report suspected ADRs that are not subject to the literature monitoring of the EMA. (64)

	<b>INTERIM-PERIOD</b>	<b>FUTURE</b>
<b>SERIOUS ADR</b>	<b>MAH:</b> a) <u>ADR occurred in the EU</u> : Report to NCA of MS where ADR occurred within 15 days. b) <u>ADR occurred not in the EU</u> : Report to EMA and (only if required in MS) also to NCAs where MP is authorised within 15 days.	<b>MAH and NCA:</b>  Report to EudraVigilance within 15 days.
	<b>NCA:</b>  Report to EudraVigilance and MAH(s) within 15 days.	
<b>NON-SERIOUS ADR</b>	<b>MAH:</b>  Report to NCA of the MS where ADR occurred within 90 days, but only if required in MS ( <i>to date only partly required by NCAs of Austria, Germany and Italy</i> )	<b>MAH and NCA:</b>  Report to EudraVigilance within 90 days.
	<b>NCA:</b>  No report required.	

Table 3: Brief overview of the general reporting requirements of post-marketing ICSRs in the EU (64)

As shown in figure 4, the number of reports received by the EMA has been constantly increasing in the past years and first exceeded the mark of 1 million ADR reports in 2013. (65)



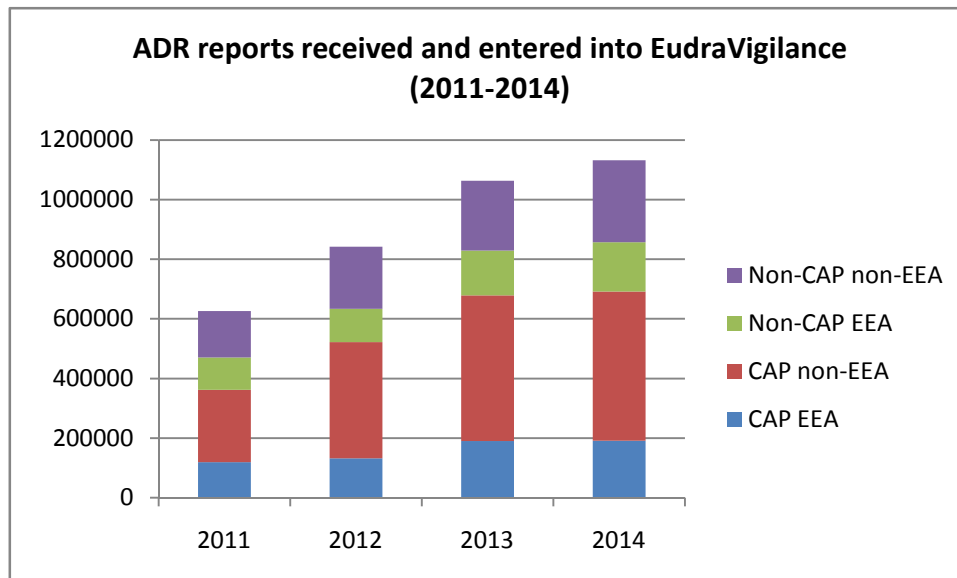


Figure 4: ADR reports received and entered into EudraVigilance from 2011-2014. (65)

#### 4.1.2 Signal management processing

Article 19 of the European Commission Implementing Regulation (EU) No 520/2012 lays down that: “[the] identification of new risks or changed risks shall be based on the detection and analysis of the signals concerning a medicinal product or an active substance.” (11) In course of the new EU PV legislation and based on GVP-Module IX, a centralised European procedure for the management of safety signals was implemented and is co-ordinated by the EMA. GVP Module IX in particular provides procedural guidance with regard to the structures, the single process steps and the roles and responsibilities of all parties involved. GVP IX characterises the signal management process by the following steps, underlining that the process is not necessarily linear as it deserves flexibility according to the specific situation:

1. SIGNAL DETECTION
2. SIGNAL VALIDATION
3. SIGNAL ANALYSIS AND PRIORITIZATION
4. SIGNAL ASSESSMENT
5. SIGNAL RECOMMENDATION FOR ACTION
6. EXCHANGE OF INFORMATION AND IMPLEMENTATION.

Especially the steps ‘Recommendation for action’ and ‘Exchange of information’ might sometimes be required at an earlier point of the process, e.g. in cases of highly probable or assured serious risks of MPs in certain patient populations.

To provide an introductory overview, the roles of the stakeholders involved in the single signal management steps are shown below:

Signal management steps	EMA, NCAs incl. lead/co-lead MSs	MAHs	PRAC	CHMP/ CMDh	EC/ NCA
Detection	X	X	-	-	-
Validation,* confirmation	X	X	-	-	-
Prioritization, analysis, assessment	-	-	X	-	-
Decision making	-	-	Recommendation**	Opinion/ Position	Decision
Regulatory action	-	X	-	-	X

\*Validated signals to be tracked in the EPITT (European Pharmacovigilance Issues Tracking Tool = access for regulators), \*\* EMA shall communicate conclusions of signal assessment to the concerned MAHs

Table 4: Overview on responsibilities in signal management processes in the EU. Source: Szmigiel A. (66)

### Role of marketing authorisation holders

According to the requirements set by the European PV legislation (cf. chapter 3.1.1 “Provisions in the European Union”) MAHs are obliged to continuously monitor the safety of their MPs marketed in Europe, in fact throughout the entire lifecycle of the MPs. It is expected that MAHs perform systematic signal detection activities, which means they shall analyse all data sources available to them (cf. chapter 2.4 “Data sources for signal detection”) and ensure that new or changed safety information with a possible relevance to the benefit-risk balance of their MPs is brought to the attention of the competent RAs in a timely manner. (67) The monitoring also includes safety data in the EudraVigilance database, at least “to the extent of their accessibility”. (5, 11)

GVP Modules VI, IX and the questions & answers document on signal management provide guidance to the MAH and specify how to proceed if a signal is detected and verified in the subsequent validation process. (5, 30, 67) Information about validated safety signals which might have “a significant impact on the benefit-risk balance for a medicinal product and/or have implications for public health” (5) is to be communicated immediately to the EMA and corresponding NCA’S as an Emerging Safety Issue. (5, 30, 67) In consideration of the strength of the safety signal and the clinical rele-

vance, the MAH might consider a proposal for regulatory action, as e.g. a change of the MP's product information. According to article 23(3) of Directive 2001/83/EC or article 16(3) of Regulation (EC) No 726/2004 respectively, the MAH is obliged to “[...] ensure that the product information is kept up to date with the current scientific knowledge [...]”. (20, 24) This also includes conclusions of PRAC assessments and corresponding PRAC recommendations which are regularly published on the “EU medicines web portal” (currently: the EMA website). (67)

It belongs to routine PV activities that the MAH further presents all validated safety signals and their status (“newly identified signals”, “ongoing signals” and “closed signals”) in the post-approval periodic benefit-risk evaluation reporting, which has to be prepared in line with ICH guideline E2C (R2). (31)

### Role of regulatory authorities

EMA and NCAs are particularly responsible for a frequent monitoring of data accumulated in the EudraVigilance database. (5, 67)

For MPs authorised according to Regulation (EC) No 726/2004 (centrally authorised MPs) the EMA collaborates with PRAC rapporteurs in order to fulfil its obligation. (5, 67) For MPs authorised in accordance with Directive 2001/83/EC (nationally authorised MPs), signal detection, validation and confirmation is performed by the NCAs of the member states where the MP is authorised. (5, 67) Because many nationally authorised MPs are approved in several European member states, e.g. in mutual-recognition or decentralised procedures, a worksharing system has been established to avoid duplicate work. Basically, one member state is appointed as lead member state to monitor active substances of nationally authorised MPs on behalf of the other member states. (5, 67) The EMA publishes the latest “*list of substances and products subject to worksharing for signal management*” on its website. (67)

To allow a proper exchange of information between the EMA and all NCAs with regard to validated safety signals, the EMA maintains the web-based database called “European Pharmacovigilance Issues Tracking Tool” (EPITT). (5) Safety signals are entered into EPITT by the RA's who validated the signals and important subsequent information (e.g. evaluations, timelines, decisions etc.) is added systematically according to the EMA guidance document “Exchange of Information Relating to Signals through EPITT by the EU Regulatory Network”. (5)

Every safety signal that has been validated and confirmed is transmitted to the PRAC for “*signal analysis and prioritisation, assessment and subsequent recommendation(s) for action*” (67). In its monthly meetings the PRAC discusses the prioritised safety signals and concludes whether there is a need for further evaluation, additional information and/ or whether any kind of regulatory actions (e.g. a change of the product information, the initiation of a referral procedure, urgent safety restrictions) are warranted at this point of time. (67) While recommendations to provide supplementary information are directly addressed to all MAHs concerned, recommendations for regulatory action are addressed to the CHMP (centrally authorised medicines) or to the CMDh and the Member States (for nationally authorised medicines). (67)

The draft agenda for each PRAC meeting, as well as detailed meeting minutes and the summarized meeting highlights are published on the EMA website. An overview of the “PRAC recommendations on safety signals” is published every month after the corresponding CHMP and CMDh meetings and is divided into three parts (68):

1. Recommendation for update of the product information, including the exact English wording and the time frame for implementation.
2. Recommendation for supplementary information to be provided by the MAH (directly or via evaluation in the periodic benefit-risk evaluation reporting).
3. Other recommendations, including e.g. no action but further monitoring and routine pharmacovigilance, update of risk management plan, direct healthcare professional communication, referral procedure, etc.

In January 2015 the EMA started to publish translations of the exact wording for updates of the product information in all official European languages (as well as Norwegian and Icelandic) (68), and thus ensures the consistency of the updated safety information throughout all Member States. Since August 2015 those official translations are even published at the same time as the corresponding “PRAC recommendations on safety signals”, which ensures that the new information can be implemented by the MAH more quickly. (68)

The EMA publishes detailed information on its workload in the annual reports, including numbers and statistics with regard to the signal detection and signal management performances. Overall, EMA’s Signal Validation Team has reviewed an average of about 2000 potential signals in the past years, the vast majority being generated from data provided by the EudraVigilance database (96% in 2012, 91 % in 2013, and 87% in 2014). (65, 69, 70) Other important sources, such as scientific literature or e.g. communication with RA’s outside of Europe (in 2012 in particular the Japanese MHLW/PMDA, but also the U.S. FDA and the WHO) are mentioned in the reports. (65, 69, 70)

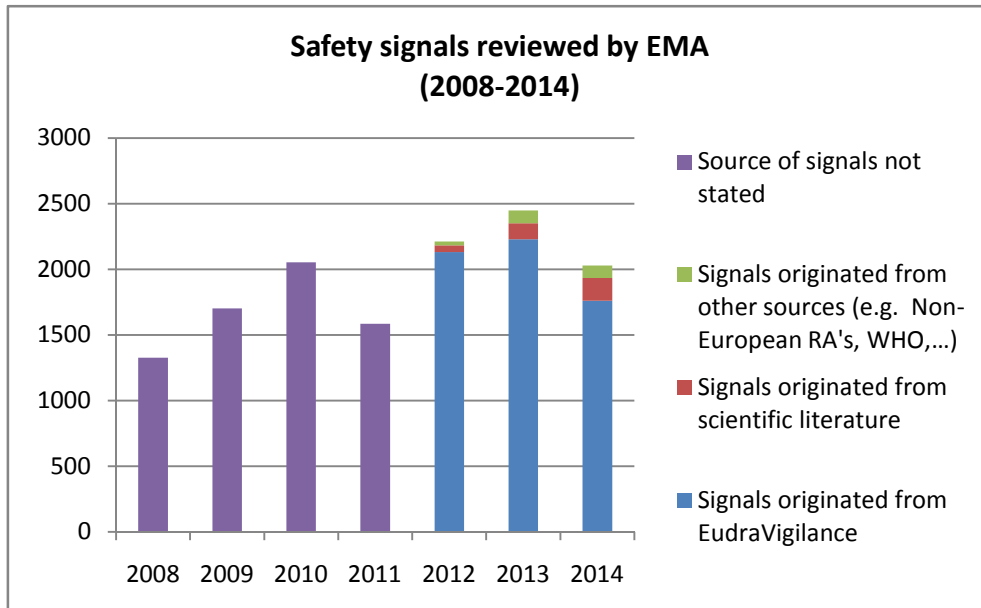


Figure 5: Potential safety signals reviewed by EMA from 2008 until 2014.

Usually about 80 % of those potential safety signals do not pass the validation step and are closed without further evaluation. (65, 69, 70) Considering the data from EMA's annual reports, only 43 safety signals in 2013 and 34 safety signals in 2014 were validated and confirmed, thus subsequently assessed by the PRAC. (65, 69) This corresponds to less than 2% of the large amount of potential safety signals reviewed by the EMA. (65, 69)

Taken together the signals detected and validated by EMA and NCAs, PRAC prioritised and analysed 100 safety signals in 2013 (thereof 43 from EMA + 57 from MS) and 90 safety signals in 2014 (thereof 34 from EMA + 56 from MS). (71, 72)

The majority of those signal assessments (around 48% in 2013 and 40% in 2014) resulted in a recommendation for an update of the product information, for some signals also including the distribution of a Direct Healthcare Professional Communication (DHPC) in order “to increase awareness about the new safety information”(72) and “highlight important new safety information to prescribers” (71). In 2013 and 2014 there was further one recommendation to change the RMP with regard to the safety signal, one recommendation to conduct a Post-Authorisation Safety Study and three signal assessments resulted in referral procedures for a further formal evaluation. (71, 72) For more detailed information on the outcomes of the previous PRAC evaluations, illustrative pie charts which depict the assessment results of 2013 and 2014 are provided in Annex B.

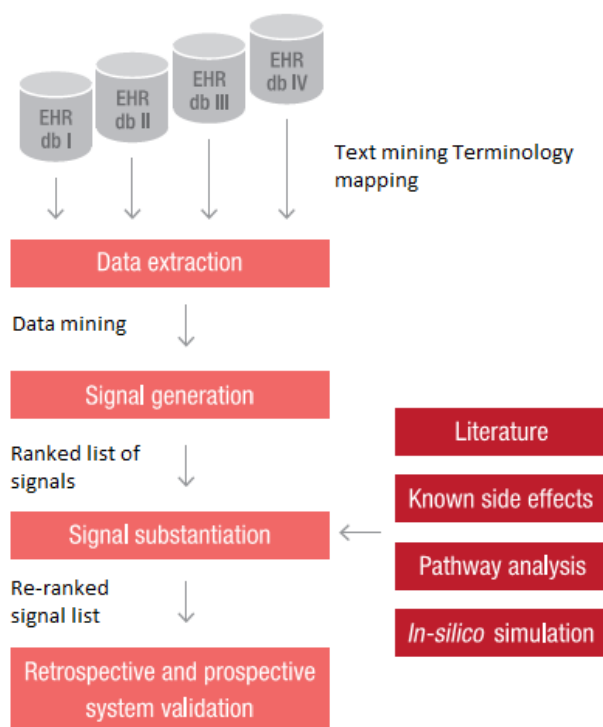
### 4.1.3 Steps towards proactive safety surveillance

#### EU-ADR project

In order to develop a more proactive approach for the detection of safety signals the EC started a pharmacovigilance initiative titled “Exploring and understanding adverse drug reactions by integrative mining of clinical records and biomedical knowledge” in 2008, also known as “EU-ADR project”. (73) The main goal was the development of “*an innovative, computerized system for the automatic detection of drug safety signals, i.e. unknown or in completely documented drug-event associations*” (74).

Different independent organisations of several European countries (Denmark, France, Spain, Italy, Netherlands, Portugal, Sweden, United Kingdom) participated from 2008-2012 and used various electronic health care record databases with medical records of more than 30 million patients to create a signal management system supplementing the existing traditional spontaneous reporting systems. (73)

#### EU-ADR System



Safety signals were generated by the use of “*data and text mining techniques, epidemiological and other computational techniques*”, validated and further assessed. (73) Substantiation processes focused on literature screenings, causality assessment and “*computational analysis of biological and chemical information (drugs, targets, anti-targets, SNPs, pathways, etc.)*” in order to validate the generated signals, to explain them and put them into context of the current state of biological knowledge. (73)

Figure 6: EU-ADR project. Source: Eva Molero et al., 2013. (75)

The final reports of the EU-ADR project have been published by the EU-ADR Consortium and provide detailed information on the data mining techniques applied, on literature and data base mining. (73)

The ‘Final Report on Retrospective Validation’ contains lists of safety signals determined during the project: one for drug-event associations with a high level of evidence (“*true positive*”) and one for signals with no supporting evidence (“*true negative*”), as shown in Annex C. (74) The performance of the EU-ADR database network is further compared in a retrospective approach with regard to the detection of safety signals against the spontaneous reporting systems of the U.S. FDA (formerly: AERS) and the WHO (Vigibase). (74) It was concluded that the EU-ADR database showed a very high specificity, similar to the two compared spontaneous reporting databases.(74) However, the spontaneous reporting databases were found to be superior with regard to the sensitivity in the generation of known safety signals, which was explained with potential “*strategies induced by regulatory actions*” to prevent the possible risks (74). A table with the results of the comparison can be found in Annex D.

#### EU-ADR Alliance

Based on the success of the EU-ADR project, the ‘EU-ADR Alliance project’ was created in 2012 with the aim of “*running studies and answering drug safety questions in a federated manner, using extracted data from multiple European EHR and healthcare databases.*” (75) The EU-ADR Alliance uses eight electronic health care record databases of Denmark, Germany, Italy, the Netherlands and the United Kingdom and in this way has access to more than 45 million patient records. (75) The project started with three studies on the following topics: “*the use of oral contraceptives, the risk of cardiac valve disorders associated with the use of biphosphonates, and the monitoring of the effectiveness of risk minimization in patients treated with pioglitazone-containing products.*” (75)

## 5 Signal management in the United States of America

### 5.1.1 Reporting requirements of ICSRs

The FD&C Act and FDA implementation regulations require post-authorisation ICSR monitoring and ADR reporting by manufacturers, packers, and distributors of concerned MPs marketed in the USA. (6, 21)

Electronic safety reporting of spontaneous ICSRs in a standardized format (ICH E2B, in xml.) is mandatory since June 2015. (19, 76) Serious, unexpected ADRs from domestic and foreign sources are to be reported to the FDA within 15 days as expedited '15-day Alert Report'. (57) All other ADRs are to be reported on a quarterly basis during the first three years following the marketing authorisation and thereafter annually in 'Periodic Adverse Drug Experience Reports'. (57)

HCPs and consumers are encouraged to voluntarily report serious ADRs, medication errors or quality problems concerning MPs regulated by the FDA. For this purpose FDA holds the 'Safety Information and Adverse Event Reporting Program' called 'Med-Watch'. (57, 77)

The Agency collects spontaneous reports on MPs marketed in the USA in the FDA Adverse Event Reporting System (FAERS). (57, 76) In the past years, the number of reports is constantly increasing and the database currently counts already more than 9 million reports since 1969. (57) ADRs related to vaccines are collected separately in the U.S. Vaccine Adverse Event Reporting System (VAERS). (78) VAERS is managed by the FDA in collaboration with the U.S. Centers for Disease Control and Prevention (CDC). (78)

The national databases present essential tools for FDA's post-authorisation safety surveillance and serve as very important sources for the detection of new safety signals. Figure 7 illustrates the U.S. post- authorisation ADR reporting on MP (excluding vaccines) and shows the way how ICSRs are collected for the FAERS database.



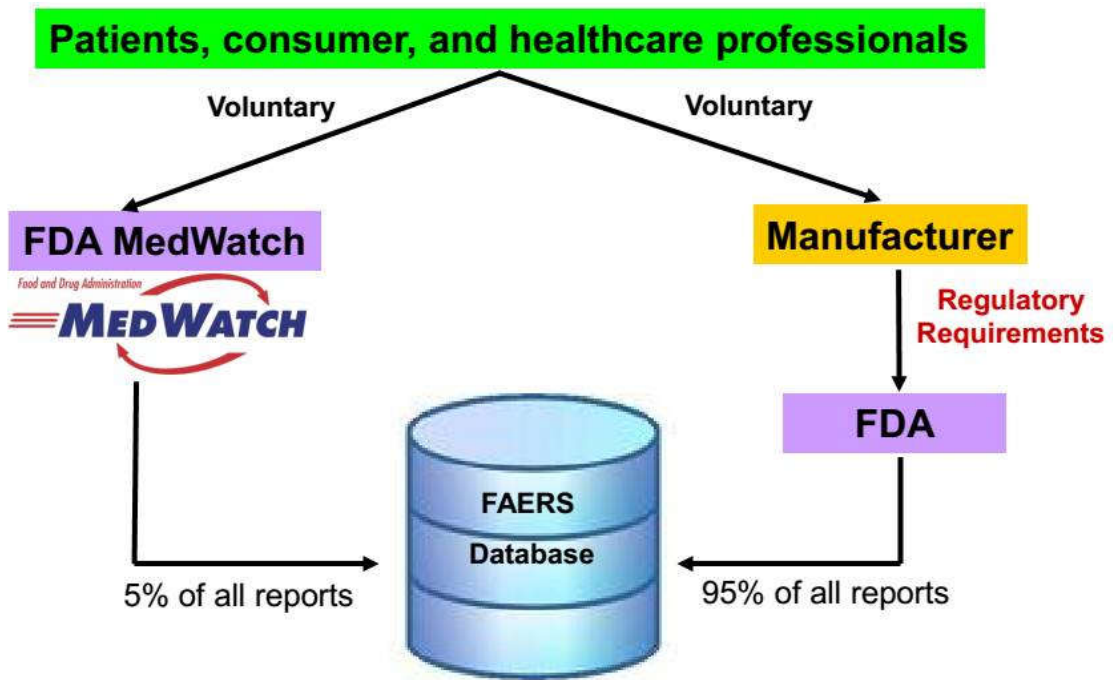


Figure 7: Post-authorisation ADR reporting in the USA. Source: FDA (57)

With millions of reports enclosed, FAERS belongs to the largest spontaneous reporting systems worldwide. The constant increase of reports received by the FDA and entered into the ADR databases is shown graphically in figure 8 below. (79)

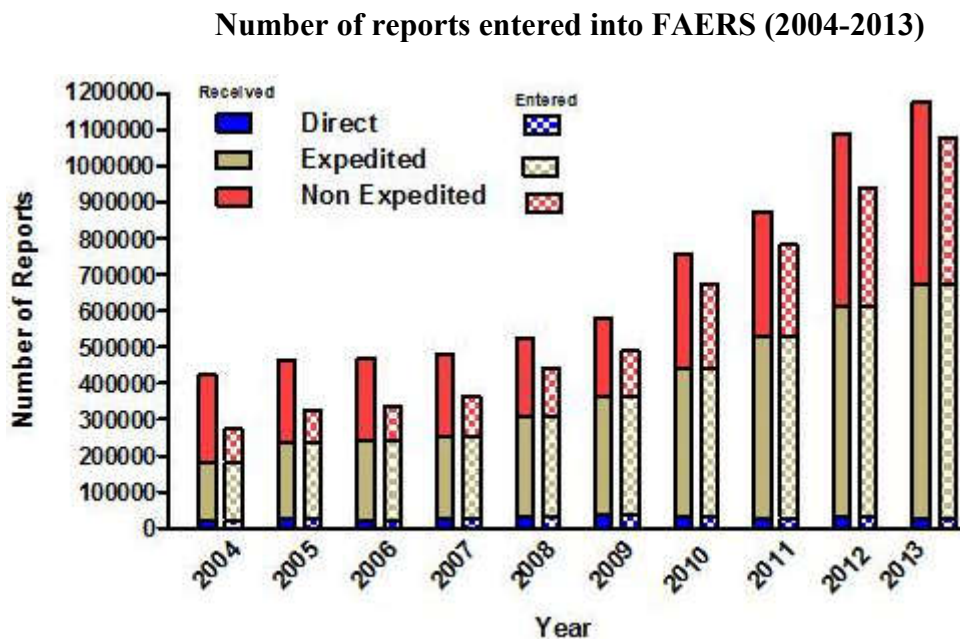


Figure 8: Number of reports received and entered into FAERS by type of report since the year 2004 through 2013. The Source: FDA (79)

### 5.1.2 Signal management processing

In the USA there is no guidance document quite alike the European GVP-Module IX, which is only dedicated to the management of safety signals and describes all process steps for every stakeholder involved. Instead, there are several guidance documents that describe the handling of safety signals and provide advice to the different parties involved. The most relevant guidance documents have been listed and briefly described above (see chapter 3.1.2). In the following, the handling of safety signals by MAH and the U.S. FDA is described.

#### Role of marketing authorisation holders

The U.S. PV Guidance ('Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment') of 2005 gives specific recommendation to industry on the identification, evaluation and further handling of safety signals. (7) MAH's are expected to analyse reported ICSRs, conduct signal detection, and carefully evaluate the safety concerns related to their MPs. The evaluation usually includes a causality assessment, including the categorization on the causal relationship (e.g. "probable", "possible" or "unlikely"). (7) If a safety signal is identified and preliminary characterized, the potential risk is to be analyzed and described, ideally taking into account additional investigation (e.g. pharmacoepidemiologic risk assessment measures). (7) For further evaluation, especially in cases of potential serious safety risks, the FDA also encourages the conduct of observational studies, as e.g. pharmacoepidemiologic studies or the review of registries or surveys. (7) In case a safety signal is associated with a potential safety risk, it is recommended to present all findings related to the safety concern to the FDA, including detailed information on analyses performed, an evaluation of the benefit-risk-ratio for the concerned patient population and, if applicable, also proposals for further investigational studies and adequate risk minimisation activities. (7) The FDA, taking into account the information received by the MAH, further conducts its own review on the safety signal in order to estimate the potential risk and decide on possible regulatory actions. (7)

#### Role of regulatory authorities

The ADRs entered into FAERS are generally monitored and evaluated by safety evaluators of the CBER Office of Biostatistics and Epidemiology/Division Epidemiology and the CDER Office of Surveillance and Epidemiology (OSE) in collaboration with the respective Office of New Drugs (OND). (39, 40, 80) As mentioned above in chapter 3.2.2, signal management activities are performed in general by staff of the CDER OSE Office of Pharmacovigilance and Epidemiology (OPE), in particular the divisions of

Pharmacovigilance DPV I & II. (56) Several teams composed of safety evaluators and medical officers analyse safety information related to MPs marketed in the USA by screening of various sources, e.g. ADR databases and scientific literature, in order to detect possible safety signals and perform a scientific, clinical evaluation and recommend regulatory action if necessary. (56, 57)

Any safety issue which could pose a potentially serious risk is entered into CDER's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) by the OSE or OND staff. (39, 41) DAARTS is a centralized system which enables the FDA to share information among the various offices. CDER MAPP 4121.2 (Tracking of Significant Safety issues in Marketed Drugs - Use of the DARRTS Tracked Safety Issues') provides guidance to the FDA staff on the management and use of DAARTS, as well as the creation of TSI's. (41) In case of the identification of a significant signal of a serious risk, a Tracked Safety Issue (TSI) is issued and the sponsor is informed. (39)

Since the introduction of DARRTS in 2007, many TSI's have accumulated and not all TSI's are equally urgent. (18) To ensure that the most important issues are addressed in a timely manner, FDA has developed a framework for categorisation of TSI's in terms of "*priority, standard, or emergency*". (18) The CDER's draft guidance on this matter 'Classifying Significant Postmarketing Drug Safety Issues' was published in 2012 and explains how FDA carries out prioritization decisions, in particular depicting the main hazard assessment criteria (relative seriousness of the safety issue, estimated size of the population exposed, suspected frequency of harm to patients), as well as different modulating factors (context of the drug's use, data quality and biologic plausibility). (18)

According to section 505 (k) (5) of the FD&C Act (21 U.S.C. 355), FDA is obliged by law to perform signal detection on a regular basis and screen FAERS fortnightly. Quarterly publication of potential safety signals on the FDA website in an early stage of the evaluation is also expected. Procedures and policies regarding FDA's 'section 921 postings' are explained in detail in the CBER SOPP 8420 ('FDAAA Section 921: Posting of Potential Signals of Serious Risk') and the CDER MAPP 6700.9 ('FDA Posting of Potential Signals of Serious Risks Identified by the Adverse Event Reporting System') respectively. (39, 40) The documents explain how relevant safety issues for the quarterly posting are to be determined by CBER and CDER staff. (40) Methodologies are depicted, clear definitions of criteria for inclusion and exclusion are given and assessment and management steps regarding the publication of potential serious safety signals are described. (39, 40)

In 2013 and 2014, the FDA has posted six potential safety issues per year under the 'section 921 postings' on potential signals of serious risks. To give an insight on the type of publication the postings of 2014 are listed in Annex E. The postings are updated

regularly according to changes in the evaluation status until the FDA decides on an initial action, e.g. the recommendation of labelling modifications, changes in the marketing authorisation or the affirmative decision that no further action is warranted. (39, 40)

According to the FDA, an early communication of relevant drug safety information to the public is of great importance to help “*professionals, patients, consumers, and other interested persons [...] to make more informed individual treatment choices*”. (37) Besides the quarterly “section 921 postings” on potential safety signals, several other methods for communication of drug safety information, e.g. ‘MedWatch Alerts’, ‘DHCP letters’, ‘Drug Safety Communications’ and ‘Safety & Availability (Biologics) Communications’, are described in the Draft Guidance ‘Drug Safety Information-FDA’s Communication to the Public’, published in 2012. (37)

With regard to the assessment of identified safety signals by DPV I & II staff it is to mention that epidemiologists from DEP I & II assist in the evaluation and provide the epidemiological perspective, e.g. by review of epidemiologic study protocols. (56) The drug utilization team further delivers additional data and information on the level of utilization and drug usage patterns e.g. by analyzing patient-based reporting rates. (56) Epidemiologic and drug utilization data support the evaluation process in order to reach an understanding of the nature and potential risk of the safety signal, especially with respect to clinical importance, Risk Evaluation and Mitigation Strategies (REMS) and the impact on possible regulatory actions. (56)

Regulatory actions are mostly associated with labelling changes, risk management programs and enhanced public communication. (56) However, if necessary the FDA might also decide that a re-evaluation of the approval or other regulatory decisions are necessary to improve the safety of the MP. (56)

Apart from the few ‘section 921 postings’, information about the annual number of safety signals processed by the FDA could not be obtained for the purpose of this master thesis.

### 5.1.3 Steps towards proactive safety surveillance

#### Sentinel Initiative

In 2008, FDA launched the Sentinel Initiative, a national electronic safety monitoring system invented to perform active post-authorisation safety surveillance of MPs regulated by the FDA. (81)

The Sentinel system was started in form of several projects, including the pilot project ‘Mini-Sentinel’: a data network of participating organizations supports the FDA since the run of the first queries in 2010 by tracking several electronic health databases containing ADR reports for possible safety signals. (82) Sentinel aims to “[enable] FDA to improve active surveillance by better understanding and more accurately estimating the incidence of a given safety risk in a relevant population.” (82)

In the interim report of 2015 (82), four successful cases of regulatory decisions majorly influenced by the Sentinel analysis are mentioned:

- **“Dabigatran.** FDA ascertained that bleeding rates associated with dabigatran, a new drug, were not significantly higher than bleeding rates associated with warfarin, an older drug, despite the large number of postmarket adverse event reports of serious and fatal bleeding events. FDA’s finding led to a safety communication and currently ongoing protocol-based assessment.
- **Rotavirus vaccine.** FDA identified that administration of rotavirus vaccine (Rotateq) led to an increased risk of intussusception (a serious abdominal condition), which was not detected during clinical trials prior to approval. Information led to an FDA label change.
- **Olmесartan.** FDA confirmed results of case studies that demonstrated increased risk of sprue-like enteropathy with long-term olmesartan use, but it did not find class effects. Findings led to FDA safety communication and label change.
- **Influenza vaccine.** FDA found no increase in risk of febrile seizures in children after receiving vaccination with Fluzone. Findings led to FDA safety communication.” (82)

The positive experience proves that the active surveillance system is becoming a vital part of FDA’s signal assessment in post-marketing safety surveillance. In the 7<sup>th</sup> annual ‘Sentinel Initiative Public Workshop’ in January 2015, the “transition from the Mini-Sentinel pilot program to the full Sentinel System” was part of the programme. (81)

## 6 Signal management in Japan

### 6.1.1 Reporting requirements of ICSRs

According to articles 68/10, 68/13 and 68/24 of the Japanese Pharmaceutical and Medical Devices Law, MAHs, clinical institutions, pharmacies and HCPs are obliged to collect and report ADRs and infections caused by MPs. (43) The ICSRs are submitted to the PMDA for further processing. (42, 43) Principal requirements and obligations with regard to the reporting format are provided in notifications issued by the MHLW, one of the most important ones being ‘PFSB Notification No. 1002 of 2 October 2014 on adverse drug reaction reports’. (45)

Electronic reporting in a standardized format is recommended in Japan and further promoted by PFSB/SD Notification No. 0917/2 of 17 September 2013 named “ADR Reporting in Post-marketing Surveillance and Clinical Trials in accordance with ICH E3B (R3).” (10) The reporting format will be adopted by April 2016 according to the specifications in the international ICH Guideline E2B (R3). (43)

The introduction of a system which enables patients for direct reporting is mentioned in the PMDA Annual Report of 2013 as part of the goals to be achieved until March 2019. (“Third mid-term targets”). (83)

Provisions regarding the time frame for expedited reporting are given in article 228/20 of the Pharmaceutical and Medical Devices Law Enforcement Regulations. (43) As in the EU and in the USA, the time frame for reporting depends on the seriousness and predictability of the ICSR. In general, serious ADRs from Japanese and foreign sources have to be reported to the PMDA within 15 days by fax and/or email and unexpected non-serious ADRs are to be reported in periodic reports. (43) Non-serious ADRs which are expected, as listed in the product information (SmPC, PIL), are not subject for reporting to the PMDA. (43) PFSB/SD Notification No. 1125010 and PMDA/OS Notification No. 1125001 of 25 November 2005 (“Periodic Reports of Unknown, Non-serious Adverse Drug Reactions to Medicinal Products”) provides details on the criteria and requirements of the periodic reporting of unexpected non-serious ADRs. (43) Usually, for MPs which have not been re-evaluated yet, such periodic reports are required every 6 month for the first 2 years after granting of a marketing authorisation as well as every 12 month thereafter. (43) For MPs which have been successfully re-evaluated they are to be submitted every 12 month as well. (43)

Since 2003 the PMDA collects reported ADRs in an electronic database called “ADR Information Management System”. (1, 84) The MHLW also has immediate access to the database. (83) Public access to selected data on the ADRs found in the database is possible via the PMDA website since 2006. (83) However, until today there is only a Japanese version available. (1, 10) The following figure depicts the constantly increasing number of reports on ADRs and infections received by the PMDA during the fiscal years 2009-2013.

### Changes in the Number of Reports on ADRs/ Infections

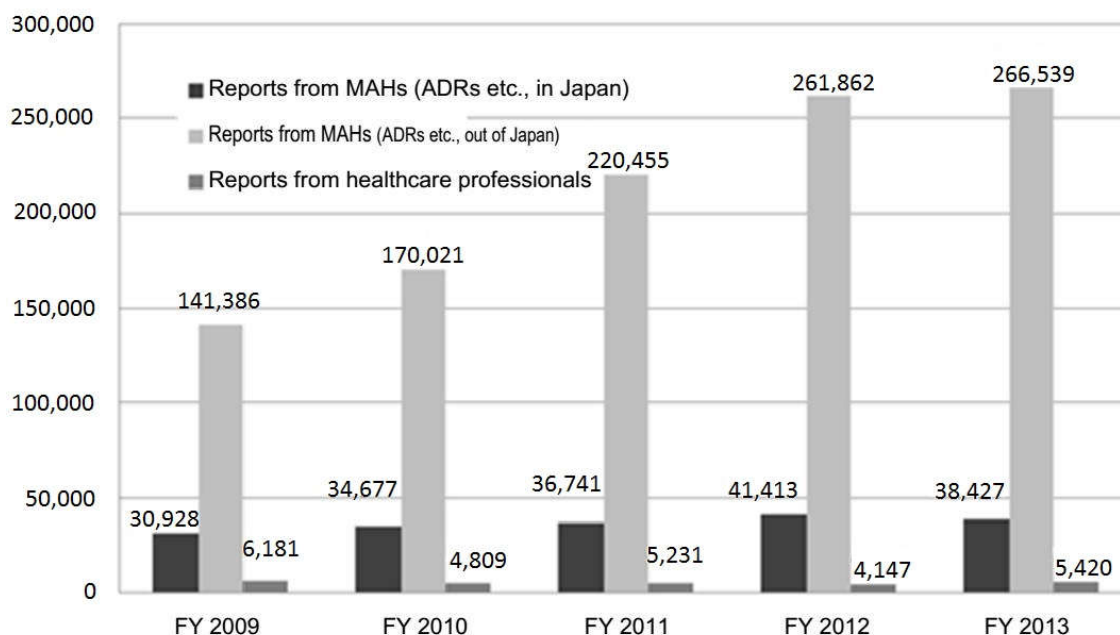


Figure 9: Numbers of reports on ADRs/Infections by source since the fiscal year 2009 through fiscal year 2013 (March 2009- April 2014). Source: PMDA, Annual Report FY 2013 (83)

#### 6.1.2 Signal management processing

As in the USA, in Japan there is no guidance document quite alike the European GVP-Module IX. Signal management activities are to be performed in compliance with the Japanese GVP Ordinance which has been described in chapter 3.1.3 above. As explained in chapter 2.1 of this thesis, the term “safety signal” is not as common in the present (translated) documents containing information about the Japanese PV systems. In comparison to the parts where the corresponding activities in the EU and the USA are explained, the current chapter might therefore comprise the signal management activities more broadly. Figure 10 provides an overview: a flowchart which depicts the processing and interaction of MAH, PMDA and MHLW with regard to the general handling of safety information in the post-approval phase. (43)

### Japanese post-approval safety surveillance

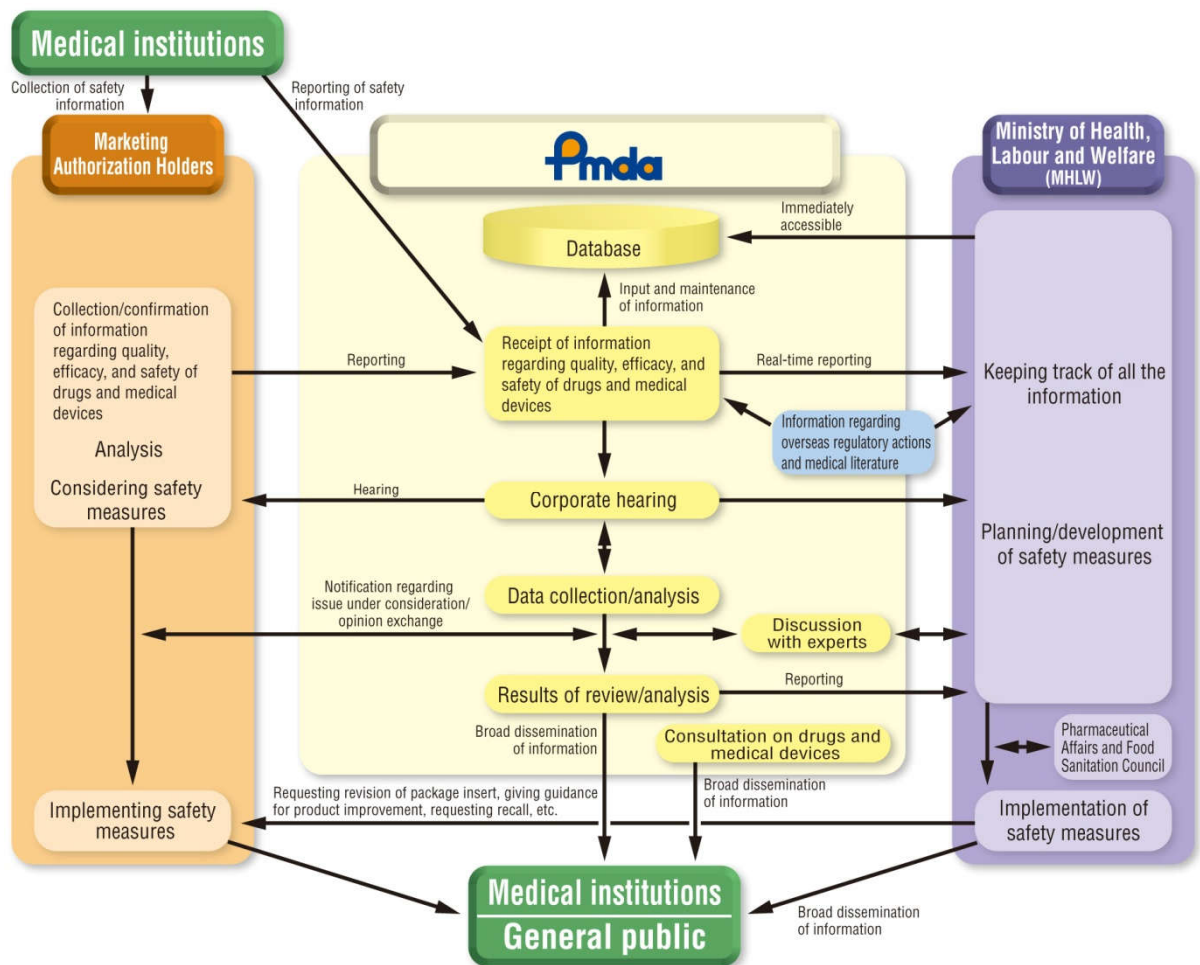


Figure 10: Safety information flow in the Japanese post-approval safety surveillance of MPs. Source: PMDA (84)

#### Role of marketing authorisation holders

After collection of safety related information of national and international sources according to the provisions of the Pharmaceutical and Medical Device Law the MAH is required to confirm the information, analyse the results and, in collaboration with the PMDA, take appropriate actions with regard to the planning and implementation of safety measures. (43)

In context with the aim for an early detection of possible safety signals, the Japanese post-approval safety surveillance system holds a unique concept called “Early Post-Marketing Phase Vigilance” (EPPV). EPPV exists since 2001 and is mandatory for prescription MPs during the first six month after the initial launch. (43, 85) To avoid preventable ADRs, the MAH is required to explain important information with regard to the appropriate and careful use of the MP to each medical institution before the first delivery and further keep them informed on a regular basis until 6 month after launch. (85)



In addition the MAH has the obligation to proactively support the collection of ADRs by constantly reminding the medical institutions to immediately report serious ICSRs under the treatment with the new MP. (85) The intensive surveillance measures demanded under EPPV are briefly illustrated in the figure below and are explained in detail in the PFSB/SD Notification No. 0324001 of 24 March 2006 (“Implementation of Immediate Post-Marketing Surveillance for the Prescription Medicinal Products”). (43)

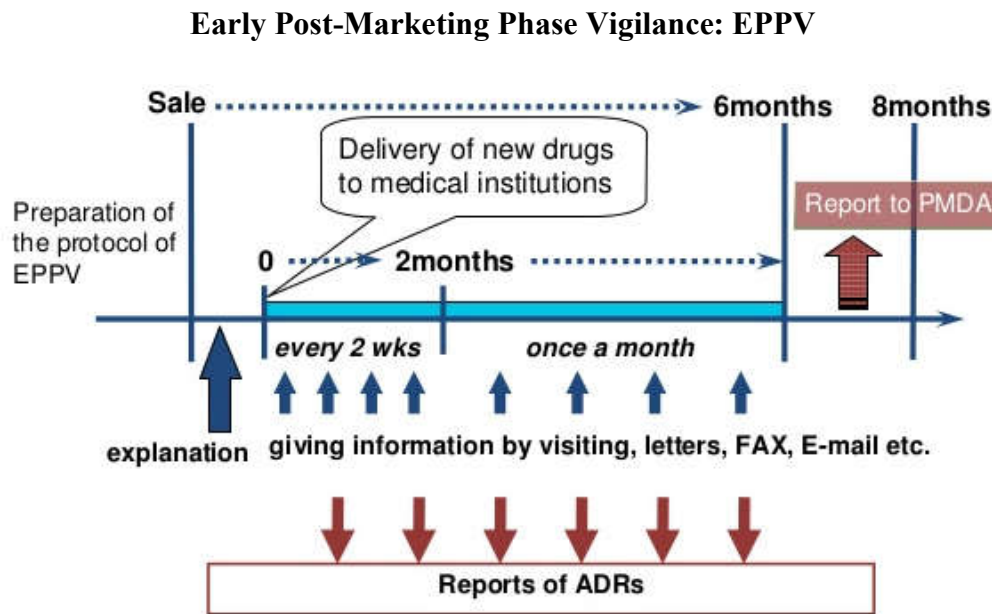


Figure 11: Illustration of Japanese ‘Early Post-marketing Phase Vigilance’ (EPPV). Source: Tomoko Okudaira (PMDA) (85)

### Role of regulatory authorities

ADRs which are received through the reporting system are collected by the PMDA Safety Department in the database of the RA. (43) The PMDA Review Department is involved in the evaluation of ADRs reported within a short time after the first marketing in connection with EPPV. (83) In addition, the PMDA performs broad literature screenings on a regular basis and places much value on the close monitoring of regulatory actions taken by foreign RAs, as e.g. the European EMA or the U.S. FDA. (43, 83) In the past years, MHLW and PMDA have made efforts to enable its staff to easily use additional data sources beyond the “traditional” ADR database, literature findings or indications on safety concerns given by foreign RA’s for safety surveillance purposes. In this context it seems important to name the “Medical Information Database- project” (MID-NET®-- project). In 2011 MHLW and PMDA have started to develop a national, Japanese network for electronic medical records: a medical information database comprising selected medical institutions and healthcare groups in order to collect more information (aim: covering ~10 million patients) for safety assessment purposes of

PMDA, MAH's or others, e.g. research organisations. (83) The project includes 7 university hospitals and 3 healthcare groups spread all over Japan, as shown in figure 12. (83) Full scale operation of MID-NET(R) was targeted for the fiscal year 2016. (83)

### Project for Developing the Medical Information Database

Hubs of the medical information database will be established at 10 university hospitals/group hospitals, etc., nationwide, with the aim of collecting large amount of data.

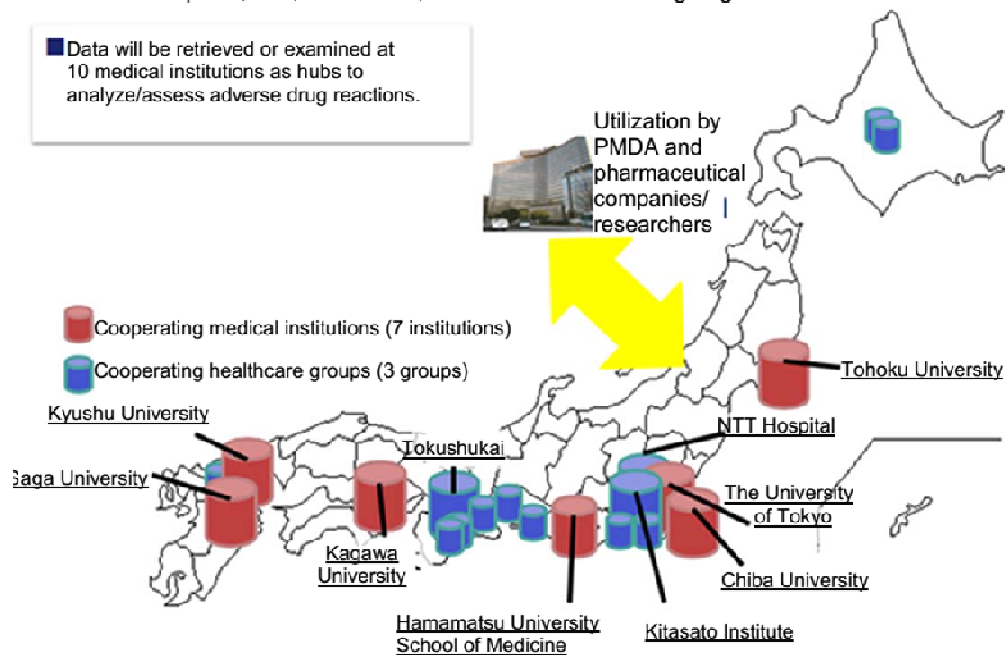


Figure 12: Hospitals participating in the Japanese MID-NET®- project. Source: PMDA (March 2014) (83)

Detailed information about the workflow of further processing in signal management activities, are exemplary given in the PFSB/SD Notice called “SOP on Handling Safety Information Which Requires a Revision of Package Insert of the Medicinal Product” of February 10<sup>th</sup> 2010. (8, 43) The SOP describes the workflow of safety related revisions of the product information, starting from the measures of safety information collection and giving an insight into the further assessment steps. (8, 43) Those steps, as illustrated in figure 10 above, basically comprise evaluations which include further investigations such as e.g. routine screenings for safety signals, the interaction with MAHs concerned and in critical cases discussions at Expert Committee meetings in order to prepare recommendations for action to the MHLW, who is responsible to implement the appropriate safety measures. (8, 43) Sophisticated data mining techniques have been implemented for signal detection purposes in the past years (in line with the “Second mid-term plan” for 2009 to 2013) and the methods are continuously reviewed by PMDA

with regard to a further improvement of the proactive part of the safety surveillance system. (83)

If it becomes clear during the evaluation of a safety concern that there is an urgent need to take regulatory measures, the safety alert might be published in form of a “Dear Healthcare Professional Letter of Emergent Safety Communication” (or “yellow letter”). (43) Important but not quite emergent safety issues are communicated via “Dear Healthcare Professional Letter of Rapid Safety Communications” (or “blue letter”). (43) The decision to publish safety information in form of a blue or yellow letter can be voluntary made by the MAH concerned or due to an MHLW order. (43)

The PMDA Annual Report of FY 2013, which at present is the last report published in English, does not provide total numbers of safety signals assessed by the RA. However, the report presents an overview on the number of post-authorisation safety measures implemented by the MHLW within April 2013-March 2014. (83) With regard to medicinal products it is stated that the MHLW has directed 160 revisions to the section “precautions” in the PIL and has published 40 messages on the PMDA website about important new safety information between April 2013 and March 2014. (83)

The PMDA website also provides information on safety concerns which are currently evaluated due to accumulated ADR data or a risk assessment of a foreign RA. (86) On September 25, 2015 for example it was posted that for the active ingredient furosemid the following risks are currently under review by the PMDA/MHLW: acute renal failure, aggravation of systemic lupus erythematosus (SLE) and interstitial pneumonia. (86)

However, the respective list provided on the English part of the PMDA website does not contain periodic entries and there are very long periods of time without any posting (e.g. Dec 2011 - Dec 2013, Dec 2013-Sept 2015). (86) This might possibly indicate that the records, at least for the English part of the website, are not maintained regularly. On the other hand, important information with regard to the safety of MPs, even including profound details of revisions (e.g. summaries of significant ICSRs leading to the change), are presented in section “Pharmaceuticals and Medical Devices Safety Information (PMDSI)” on the PMDA website and are updated monthly. (87) English translations are available as well, although PMDA does not provide any guarantee of consistency. (87)

Detailed data about the annual number of safety signals processed by the PMDA could not be obtained for the purpose of this master thesis.

### 6.1.3 Steps towards proactive safety surveillance

#### Medical Information for Risk Assessment Initiative (MIHARI project)

In 2009 the PMDA has started the “Medical Information for Risk Assessment Initiative“, known as “MIHARI project”. (83, 88, 89) The project comprises an intensive analysis of different types of electronic medical data and the detailed investigation of sophisticated signal detection methods. (83, 88, 89) It was initiated with the objective “to develop a new safety assessment system for post-marketing drugs using Japanese medical databases” (88) and to introduce more data sources to the signal management system. (83, 89) Covered by the MIHARI project, various studies have been conducted on characteristics, usability, limitations, etc. of different kind of data sources (e.g. claim data, diagnosis procedure combination data, electronic medical record data), as well as different signal detection methodologies (e.g. diverse pharmacoepidemiological methods or data mining techniques). (83, 88, 89) The following figure is taken from PMDA’s Annual Report of FY 2013 and highlights the target of the “MIHARI-project”: the introduction of new databases to enhance PMDA’s safety surveillance.

#### Study for Introducing New Databases for the Drug Safety Evaluation Process

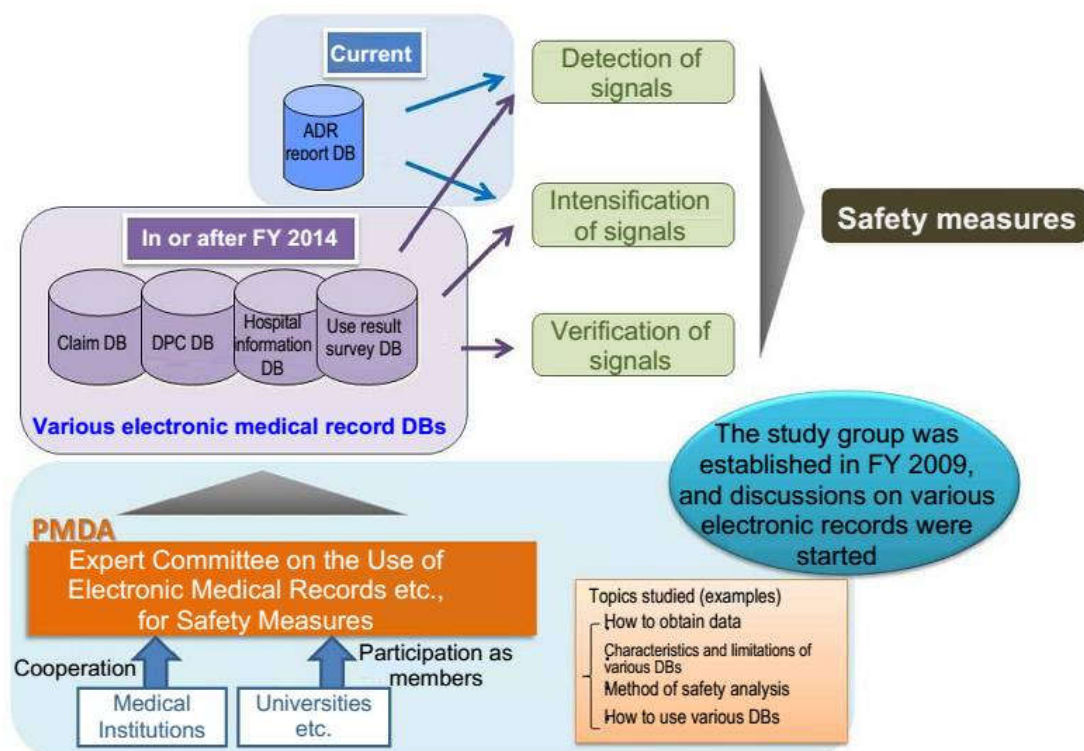


Figure 13: Study for introducing new databases to enhance PMDA’s safety surveillance processing. Source: PMDA (March 2014) (83)

### Asian Pharmacoepidemiology Network (AsPEN) initiative

Japan belongs to the founding countries of the Asian Pharmacoepidemiology Network (AsPEN), an international research network dedicated to active post-authorisation safety surveillance in order to “provide a mechanism to support the conduct of pharmacoepidemiological research and to facilitate the prompt identification and validation of emerging safety issues among the Asian countries.” (90) AsPEN was formed by Japan, Taiwan, Korea, and Australia in 2009 and recently also collaborates with China, Hong Kong, Korea, Singapore, Sweden, Thailand and the USA. (91) The network uses several databases of the participating countries, including for example claims databases, registries and electronic health records. (92, 93) Japanese datasets provided have been e.g. the ‘Japan Medical Data Centre insurance claims database’ and the ‘Hamamatsu Medical University database’. (93)

In the past years the AsPEN initiative amongst others has performed prescription sequence symmetry analyses with regard to the following specific safety concerns:

- **Antipsychotics and acute hyperglycaemia:** although the results were inconsistent across the participating countries, “a trend towards increased insulin initiation following olanzapine initiation” and “[null] or negative associations [...] for other antipsychotic medicines and insulin initiation” was found. (93)
- **Thiazolidinediones and cardiovascular diseases:** “The risk of both oedema and heart failure with thiazolidinediones was higher in predominantly Caucasian countries than in the Asian countries assessed.” (94)

## 7 International collaboration and cooperation

All three ICH regions have a longstanding history of international cooperation with other RAs on a global level by sharing important information on the evaluation of marketing authorisations, always with regard to quality, efficacy and safety of MPs. (95) Confidentiality arrangements between the EC, the EMA, the U.S. FDA and the MHLW/PMDA are in place for several years and have already been extended or renewed various times. (96, 97) Meetings, so-called ‘clusters’, are usually held via teleconferences on a regular basis, although also ad-hoc if deemed necessary. (95) The exchange of information concerns regulatory aspects of all kinds, e.g. with regard to legislation and guidance but also product- or issue-related e.g. with regard to clinical data for new applications, extensions of indications, the evaluation of safety signals or other safety information to be discussed in the context of risk-management plans. (95)

Concerning PV issues collaboration between the FDA and the EMA in form of regular teleconferences exists since 2003 and it was not until 10 years later the ‘official PV cluster’ was founded in 2013. (95) The intense communication contains the exchange of information and expert views in particular with focus on urgent safety issues and the anticipated regulatory measures, but also on general queries related to legislation and guidance, PV systems, inspections, etc. prior to the regulatory decision. According to the guiding principles of the PV cluster, “[the] primary goal of the international pharmacovigilance cluster is to support regional risk assessment with a view to enriching the decision-making phase and to facilitate international coordination of regulatory action, in particular as regards timing of public communication.” (98)

### 7.1 WHO Programme for International Drug Monitoring

The WHO Programme for International Drug Monitoring (PIDM) is a global PV network which was founded following the thalidomide-tragedy. In 1968, ten WHO members set up PIDM to jointly collect data on adverse drug reactions in a systematic way in order to detect potential safety issues as early as possible. (99) The awareness of drug safety issues has been increasing on a global level and throughout the years more countries joined PIDM. By summer 2015, more than 120 countries worldwide, including ‘industrial countries’ as well as ‘low-income countries’, are taking part on the PIDM. (99)

### Members of the WHO Programme for International Drug Monitoring (1968 – 2015)



Dark blue = Full member; pale blue = Associate member

Figure 14: Members of the WHO Programme for International Drug Monitoring (1968-2018). Source: WHO (100)

Participating countries are required to be represented by a national PV centre which holds at least a basic PV system for the collection and evaluation of ICSRs and the frequent transmission of the reports to the UMC in a defined format. (101) All member states of the European Union, Japan and the United States participate as well. Some European countries and the USA even belong to the founding members of the programme. Annex F provides a list of the participating European countries, Japan and the USA, including the respective year of joining the PIDM.

The WHO Collaborating Centre for International Drug Monitoring, known as ‘Uppsala Monitoring Centre’ (UMC) in Sweden, is in charge of the operational part of PIDM. (102) UMC manages the global PV database called ‘VigiBase<sup>TM</sup>’. (103)

In VigiBase<sup>TM</sup>, all ICSRs submitted by national PV centres participating in the PIDM are collected and achieved. (103) With more than 11 million cumulative case reports dating back to 1968, VigiBase<sup>TM</sup> belongs to the largest ICSR database in the world (*status: Mai 2015*). (103)

Especially during the last decade the database has grown extensively. From 2005 until 2015 the number of reports included has about tripled. (104) However, the reporting rates differ widely and depend very much on the country and the strength of the national PV systems. The following graph, which was published by UMC, reveals that over 80% of all cases recorded were reported from only 10 member countries and almost 50% are derived solely from the USA. (104)

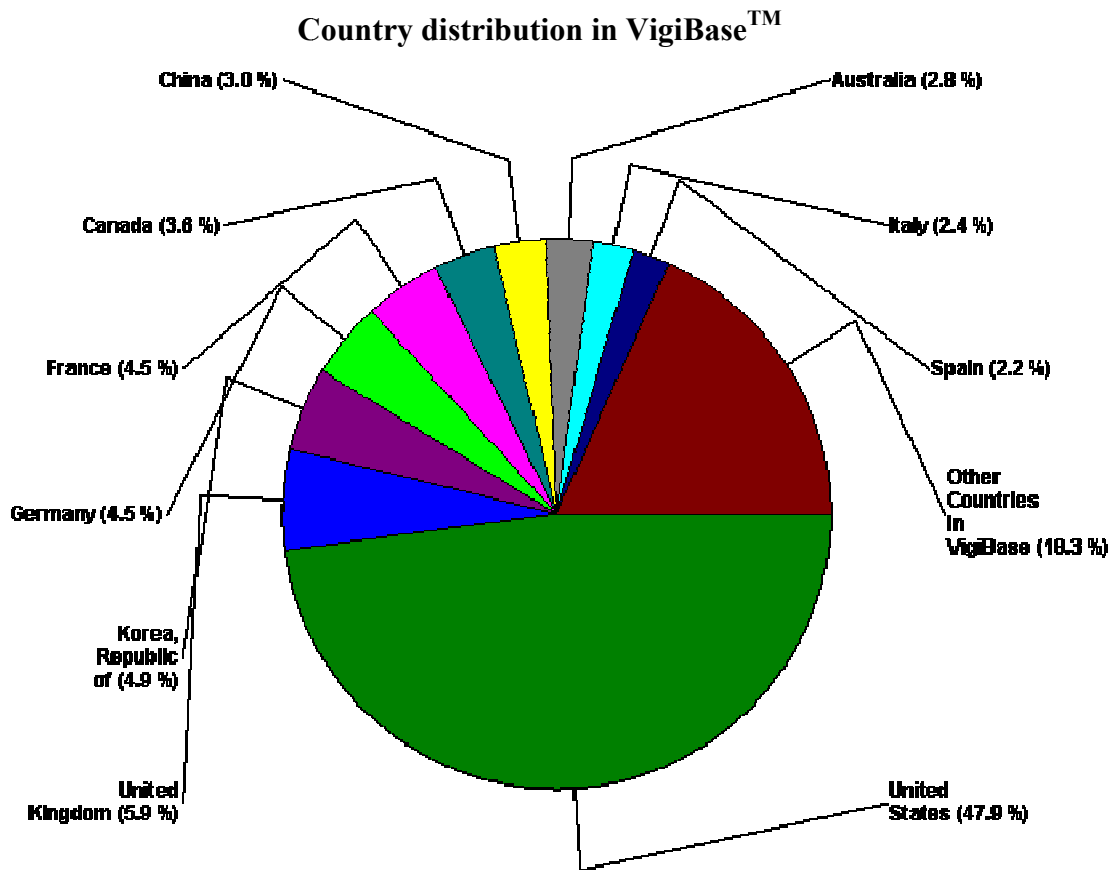


Figure 15: Country distribution in VigiBase™ (01.01.1967- 27.05.2015). Source: UMC (104).

The large data volume in VigiBase™ is regularly screened and analysed by UMC in order to identify potential safety signals. UMC also uses different computerised mathematical and statistical analysis methods, so called data-mining approaches, to perform signal detection and support the clinical assessment by PV experts. (102, 105)

WHO, UMC and the national PV centres share and exchange information through an internet forum called 'Vigimed'. (106) With respect to findings related to potential safety signals, UMC publishes a newsletter titled 'SIGNAL'. (107) The newsletter is mainly to inform members of the UCM Review Panel and collaborating national PV centres about significant findings in the area of safety signals. (107) Since February 2012, information about safety signals is also included in the 'WHO Pharmaceuticals Newsletter'. (107) It is issued about every two month and can be downloaded on the website or subscribed via email by anyone interested. (108)

Since April 2015 it is further possible for anyone interested to search VigiBase™ for statistical data on the ADRs collected by UMC with the web-based PV-tool 'VigiAccess™'. (109) By this means the WHO promotes the global communication of safety signals for MPs.



## 8 Discussion and Conclusion

The competent RA's in the three ICH regions, EU, Japan and USA, have made significant progress in the past years in reinforcing their post-authorisation safety surveillance systems, including an accelerated identification and processing of potential safety signals, increasingly efficient procedures and more pre-emptive approaches. Amongst others this has been achieved by several legislative amendments in order to increase the vigilance of the PV systems and hereby enhance the safety of MPs and deliver an improved protection of public health.

In the EU a well structured signal management procedure has been developed within the regulatory framework of the new PV legislation. The new signal management processing was introduced by GVP Module IX in July 2012, comprising a highly organised procedure in which all involved parties of the European PV network have received clearly defined roles and responsibilities. EMA, NCAs and MAHs perform signal detection on a regular basis and the scientific committee dedicated to the monitoring and evaluation of safety related issues, the PRAC, is in charge of prioritization, analysis and assessment of all validated and confirmed safety signals. The European regulatory network system 'EudraVigilance' is further being enhanced in order to permit an even more efficient safety monitoring. As part of the 'EudraVigilance' system, ICSRs of all 28 European member states are going to be centralised in one European database.

The U.S. FDA has been provided with an increased authority concerning post-authorisation safety surveillance matters, in particular by the last two reauthorisations of the PDUFA in 2007 and 2012. Management and communication of safety signals was statutory strengthened, as the regular screening of the national ADR database ('FAERS') on possible safety signals and the periodical publication of all significant findings has become a legally imposed task of the FDA. The modernisation of certain processes in the field of PV, in particular with regard to the IT-infrastructure in order to enhance quality and efficacy of safety monitoring performances as well as risk assessment procedures, was made a further goal.

In Japan the recent 'Law for Partial Revision of the Pharmaceutical Affairs Law' of 2013 also included amendments to strengthen the post-authorisation safety surveillance system. With regard to post-approval safety surveillance the PMDA has been made responsible for the collection of ICSRs as well as the further processing. The Japanese PMDA is likewise smaller compared to the EMA or the FDA. However, the number of employees working in the PMDA safety department has increased significantly in the past years and almost doubled from 82 employees in April 2009 to 152 employees in April 2014 (cf. Annex A). This underlines the importance of the assigned PV activities

and demonstrates an increased governmental awareness as well as the growing workload in this field.

During the past decades international initiatives, e.g. ICH and CIOMS, have elaborated a far-reaching harmonisation of standards and definitions in pharmaceutical sciences. In the field of post-authorisation safety surveillance this included e.g. harmonized ADR reporting formats (ICH-E2B), certain electronic standards (e.g. xml-format for message transfer), and standardised medical terminologies (MedDRA). CIOMS VIII developed general points to consider in signal management, showed different approaches to signal detection and discussed strategies to interpret signal assessment results. The responsibilities of MAH's in the three ICH regions with respect to the collection and reporting of ICSR as well as the clinical evaluation of the suspected ADRs are quite comparable. The harmonisation of standards and definitions ensures a common understanding, promotes uniform methodologies and warrants the consistency of pharmaceutical safety information in the globalized environment, thus laying the cornerstone for a better international cooperation and also the development of effective strategies in order to avoid potential duplication of efforts.

The global trade of MPs has an intense effect on PV and international cooperation in the area of safety monitoring becomes increasingly important. All three ICH regions have a longstanding history of international collaboration and cooperation, have confidentiality arrangements in place and meet on a regular basis to discuss various topics concerning the quality, safety and efficacy of MPs. Within the context of global cooperation the WHO PIDM plays a vital role with regard to the detection of safety signals. International ICSR data from currently more than 120 countries is jointly collected to form one of the largest ADR database in the world. The database allows the performance of complex, modern quantitative signal detection methodologies in order to identify and assess potential safety signals. Not only RAs of highly developed countries (as e.g. the three ICH regions) participate in the program, but also countries with less advanced PV systems which currently have only little or even no possibilities to carry out safety surveillance activities. The international collaboration and cooperation also serves to avoid duplication of work by different RAs and supports, together with a certain degree of international consistency, the enhancement of the scientific quality as well as the overall effectiveness of evaluations and assessment procedures.

The general handling of ADR processing and signal management by RAs indicates similarities as well as differences in the three ICH regions. The switch from paper-based ICSR towards electronic ADR reporting has formed the basis for a much faster processing and evaluation of safety signals, as potential safety concerns can be detected more quickly. Whereas in the EU an electronic ADR reporting is mandatory since 2005, the U.S. FDA followed only recently and made electronic reporting obligatory as of June

2015. In Japan on the other hand, a paper-based submission is further possible, although the electronic submission is strongly promoted in guidance documents. Nevertheless, the trend in the ICH regions clearly goes towards more rapid and more efficient assessment procedures resulting in appropriate regulatory actions without time delay.

In the EU, Japan and the USA the reported ADRs are collected in large national electronic databases, which are managed and maintained to provide a variety of evaluation options. The overall increasing number of reported ADRs in the past years is certainly a result of recent legislative amendments in those regions, but might as well be interpreted as an intensified commitment of HCPs to report cases of suspected ADRs to MAHs and/or RAs. With the increasing number of authorised MPs, governmental and public awareness has grown in the past years and general expectations concerning a “preferably harmless” use of MPs are high. It is expected that reliable, well-understood safety profiles are elaborated and maintained to ensure that nature and frequency of ADRs are known as soon as possible to be considered as potential risk factors in therapeutic decisions.

Clinical review and analysis of ICSR data are usually performed by PV experts in the safety departments of the RAs and support is provided by statistical signal detection methodologies, such as different kinds of data mining algorithms. The quantitative analyses applied to the safety data vary in the different RAs, but they also depend on the local IT infrastructure and the data available. RAs of the three ICH regions have further laid more and more attention towards an active surveillance and the analysis of existing data not only from spontaneous reporting data but also from other information sources, such as e.g. electronic healthcare records, different kind of medical registries or administrative claims data. Examples for active surveillance systems are the Sentinel project in the USA, the EU-ADR-project/EU-ADR-alliance, the ASPEN initiative of a consortium of Asian countries or the emerging MIHARI project of the Japanese PMDA. With the aid of those active surveillance systems several safety signals could be generated and verified already and in a small number of cases this has even led to regulatory actions, such as e.g. communication to HCPs or updates of product information. However, although such analyses are always supported by modern electronic methods and many parts of the workflow are carried out automatically, the efforts to come to useful and clinical relevant outcomes should not be underestimated as there are still significant limitations to be considered at the time of interpretation of results.

Taken together, one of the priority targets of modern pharmaceutical PV systems is the continuous enhancement of post-authorisation safety surveillance with highly efficient procedures and more pre-emptive approaches. This involves in particular an early and fast identification of important safety signals followed by rapid and rational safety

assessments, especially if risks are identified and updates of the product information or other risk minimisation measures seem advisable.

In contrast to the EU, Japan and the USA do not provide regulatory documents describing the entire signal management process as detailed as the European GVP module IX. However, signal management activities are conducted in all of the three regions, even though carried out to a different extent. After introduction of the new signal management system the EU might be ‘one step ahead’. EMA alone validated around 2000 potential safety signals annually during the past years; further signals were processed by the RAs of the European member states with the corresponding jurisdiction. Since its foundation in 2012 the PRAC assessed, based on a prioritization scale, up to 100 confirmed safety signals each year and presented a range of different recommendations for regulatory action as results (cf. Annex B). The U.S. FDA also maintains a highly sophisticated signal management system with advanced statistical signal detection techniques and assessment methodologies. However, the amount of potential safety signals published in FDA’s ‘section 921 postings’ is rather small (cf. Annex E for postings of 2014), compared to the numerous potential signals handled by PRAC. Besides its own efforts in the detection of new safety signals, the Japanese PMDA emphasizes the screening of regulatory actions of foreign RAs and maintains a tight international collaboration, especially but not limited to the field of PV. In order to compare the efficiency of the signal management systems in the three ICH regions more accurately, additional data for Japan and the USA is deemed indispensable, in particular with respect to the annual number of validated and evaluated safety signals and additional information concerning the outcomes of those assessments.

Despite present difficulties with limiting factors regarding the interpretability of results, the gradual integration of pre-emptive safety surveillance projects to enhance a faster generation and substantiation of safety signals from data other than spontaneous reporting is an emerging trend and appears to be an expanding field in the post-authorisation safety surveillance systems of all three ICH-regions. Additional intensive development in this area is planned by the operators, in particular with regard to methodologies and effectiveness. Maturely operating proactive safety surveillance systems which reliably accelerate and support the decision making processes in RAs might be expected within a few years.

It has become evident that in the era of a globalised world international collaboration and cooperation is of great importance for efficient post-authorisation safety surveillance systems. Further harmonisation of definitions and standards and a tight collaboration with regard to the exchange of safety information and scientific expertise, as well as the joint development of best practices on an international level represent the basis for opportunities towards further development in the future.

## 9 Executive Summary

During the development of medicinal products it is not possible to identify all potential safety concerns. Especially less frequent adverse drug reactions are unlikely to be observed during the clinical development, which is mainly due to the limited number of patients treated. For this reason post-authorisation safety surveillance is of paramount importance to ensure patient safety.

The essential tasks in post-authorisation safety surveillance are the identification of new or changing safety concerns and the subsequent, systematic evaluation followed by adequate action with regard to risk minimization activities. The detection of potential safety signals presents an early stage in the examination of possible safety concerns. Typically the need for further evaluation is justified, but it is not clear if a “real” risk with clinical relevance exists and if any regulatory action is warranted. The management of safety signals can be regarded as the basis of pharmacovigilance activities and belongs to the most important performances in post-authorisation safety surveillance systems.

The European Union, Japan and the United States of America, the founding members of the International Conference on Harmonisation (ICH), have established pharmaceutical regulatory systems of the highest level worldwide. Their pharmacovigilance systems are not only based on long-standing experiences, but also on empirical knowledge gained from intensive international collaboration and cooperation. The competent regulatory authorities have made significant progress in the past years in reinforcing their post-authorisation safety surveillance systems, including an accelerated identification and processing of potential safety signals, increasingly efficient procedures and more pre-emptive approaches. Amongst others this has been achieved by several legislative amendments in order to increase the vigilance of the pharmacovigilance systems and hereby enhance the safety of medicinal products and deliver an improved protection of public health.

The present master thesis intends to provide an insight into the post-authorisation safety surveillance for medicinal products in the European Union, Japan and the United States of America and constitute a comparison of the signal management systems in the three ICH regions.

## Annex A: PMDA Staff April 2009- April 2014

### Number of Executives and Regular Employees

	April 1, 2009	April 1, 2010	April 1, 2011	April 1, 2012	April 1, 2013	April 1, 2014
Total (including executives)*	521	605	648	678	708	753
Review Department**	350	389	415	438	460	492
Safety Department***	82	123	133	136	140	152
Relief Department	32	34	34	33	33	33

\* The total number includes 6 executives (including one part-time auditor). However, the total number of executive was 5 as of April 1, 2014.

\*\* The Review Department consists of the Director of the Center for Product Evaluation, Associate Executive Directors, Associate Center Directors (except the one responsible for the Office of Regulatory Science), Advanced Review with Electronic Data Promotion Group, Office of International Programs, International Coordination/Liaison Officers, Office of Review Administration, Office of Review Management, Office of Standards and Guidelines Development, Offices of New Drug I to V, Office of Cellular and Tissue-based Products, Office of Vaccines and Blood Products, Office of OTC/Generic Drugs, Offices of Medical Devices I to III, Office of Non-clinical and Clinical Compliance, Chief of Kansai Branch, Consultation Division of Kansai Branch, principal senior scientists, and senior scientists.  
In addition to the executives mentioned above, two executives serve as Deputy Center Directors (non-permanent appointment for a specified period) in the Review Department: one responsible for cellular and tissue-based products and the other for medical devices.

\*\*\* The Safety Department consists of the Chief Safety Officer, Offices of Safety I and II, Office of Manufacturing/Quality and Compliance, and Inspection Division of Kansai Branch.

Table 5: Overview on the PMDA Staff (April 2009- April 2014) Source: PMDA (63)

## Annex B: Outcomes of PRAC signal assessments in 2013 and 2014

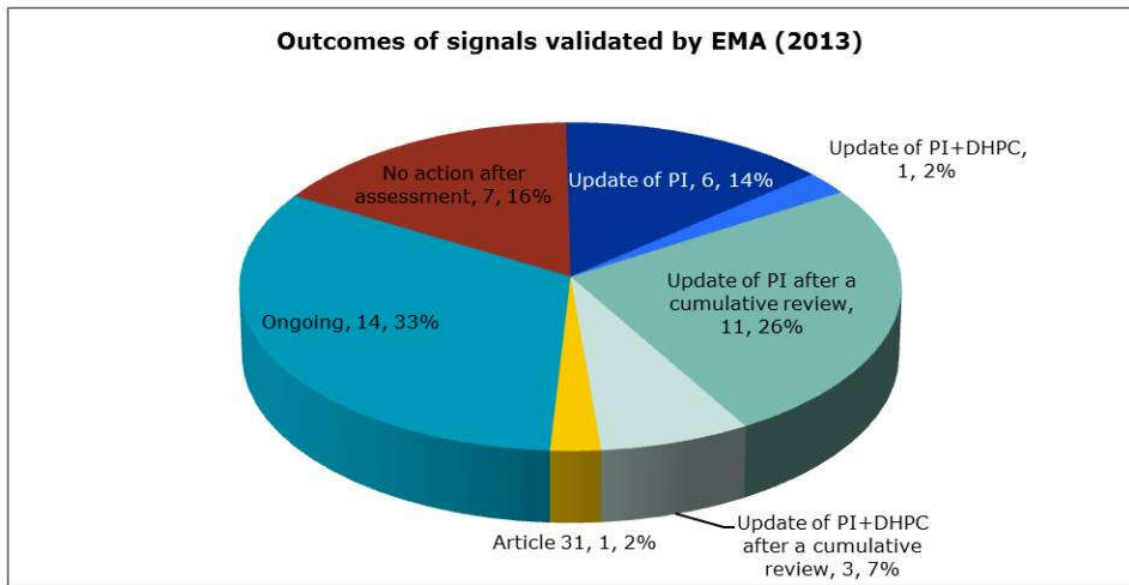


Figure 16: Outcomes of PRAC signal assessments (2013). Source: EMA (69)

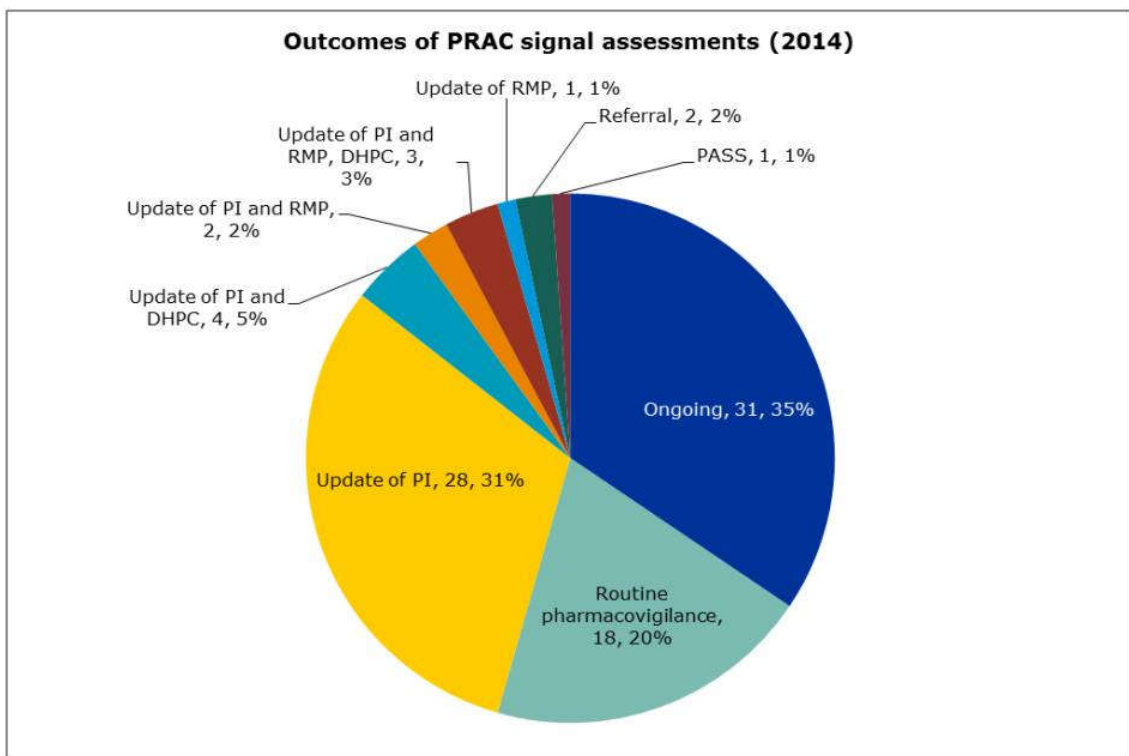


Figure 17: Outcomes of PRAC signal assessments (2014). Source: EMA (65)

## Annex C: Safety signals determined in the EU-ADR project

Event	True Positive Associations	
	ATC	Name
Acute Liver Injury (ALI)	N03AF01	Carbamazepine
	N03AG01	Valproic acid
	M01AX17	Nimesulide
	J01CR02	Amoxicillin and clavulanic acid
	A07EC01	Sulfasalazine
Acute Myocardial Infarction (AMI)	M01AH02	Rofecoxib
	A10BG02	Rosiglitazone
	G03AA07	Levonorgestrel and estrogen
	N02CC01	Sumatriptan
	M01AH03	Valdecoxib
Acute Renal Failure (ARF)	C09AA01	Captopril
	M01AE01	Ibuprofen
	N02BE01	Paracetamol
	J01MA02	Ciprofloxacin
	N05AN01	Lithium
Anaphylactic Shock (AS)	B01AC06	Acetylsalicylic acid
	N02BE01	Paracetamol
	J01CA04	Amoxicillin
	J01MA02	Ciprofloxacin
	M01AB05	Diclofenac
Bullous Eruptions (BE)	N03AF01	Carbamazepine
	J01EE01	Sulfamethoxazole and trimethoprim
	N03AX09	Lamotrigine
	M04AA01	Allopurinol
	C03CA01	Furosemide
Cardiac Valve Fibrosis (CARDFIB)	No drug with sufficient exposure that satisfies criteria for True Positive	
Neutropenia (NEUTROP)	H03BB02	Thiamazole
	B01AC05	Ticlopidine
	C09AA01	Captopril
	N03AF01	Carbamazepine
	N03AG01	Valproic acid
Aplastic anemia/ Pancytopenia (AA)	B01AC05	Ticlopidine
	N03AF01	Carbamazepine
	H03BB02	Thiamazole
	M04AA01	Allopurinol
	C09AA01	Captopril
Rhabdomyolysis (RHABD)	C10AA07	Rosuvastatin
	C10AA05	Atorvastatin
	C10AA03	Pravastatin
	C10AA01	Simvastatin
	N02BA01/B01AC06	Acetylsalicylic acid
Upper Gastrointestinal Bleeding (UGIB)	M01AB01	Indometacin
	B01AB01	Heparin
	H02AB06	Prednisolone
	M01AE01	Ibuprofen

Table 6: Drug-event associations with high evidence in the EU-ADR analysis (“true positive”).  
Source: Gianluca Trifirò, EU-ADR Consortium 2011 (74)



Event	True negative associations	
	ATC	Name
Acute Liver Injury (ALI)	R03AC13	Formoterol
	S01ED05	Carteolol
	G04CA03	Terazosin
	N04BA02	Levodopa and decarboxylase inhibitor
	C01DA02	Glyceryl trinitrate
Acute Myocardial Infarction (AMI)	A10AD01	Insulin (human)
	B03AA07	Ferrous sulfate
	J01CR02	Amoxicillin and clavulanic acid
	J05AB11	Valaciclovir
Acute Renal Failure (ARF)	C10AB04	Gemfibrozil
	R01AD09	Mometasone
	H03AA01	Levothyroxine sodium
	R06AX26	Fexofenadine
	N04BA02	Levodopa and decarboxylase inhibitor
Anaphylactic Shock (AS)	B03AA07	Ferrous sulfate
	N06AX11	Mirtazapine
	H03AA01	Levothyroxine sodium
	C02AC01	Clonidine
	C02CA04	Doxazosin
	N05BA04	Oxazepam
Bullous Eruptions (BE)	C01BC03	Propafenone
	C07AB03	Atenolol
	R03BB01	Ipratropium bromide
	R03BB04	Tiotropium bromide
Cardiac Valve Fibrosis (CARDFIB)	C08CA02	Felodipine
	N06AB08	Fluvoxamine
	L04AX03	Methotrexate
	C09CA04	Irbesartan
	C03CA01	Furosemide
Neutropenia (NEUTROP)	G03CA03	Estradiol
	C07AA07	Sotalol
	H03AA01	Levothyroxine sodium
	C10AA05	Atorvastatin
	C10DA14	Isosorbide mononitrate
Aplastic anemia/ Pancytopenia (AA)	G04CA02	Tamsulosin
	C09CA04	Irbesartan
	C10AA04	Fluvastatin
	S01EE01	Latanoprost
	S01ED01	Timolol
	R06AX27	Desloratadine
Rhabdomyolysis (RHABD)	R06AX26	Fexofenadine
	G03CA03	Estradiol
	C02CA04	Doxazosin
	A10BB12	Glimepiride
Upper Gastrointestinal Bleeding (UGIB)	S01ED01	Timolol
	C01DA02	Glyceryl trinitrate
	R06AX26	Fexofenadine
	C10AA01	Simvastatin
	S01EC03	Dorzolamide
	L02AE03	Goserelin
	N05CF01	Zopiclone

Table 7: Drug-event associations with no evidence in the EU-ADR analysis (“*true negative*”). Source: Gianluca Trifirò, EU-ADR Consortium 2011 (74)

## Annex D: Comparison: EU-ADR system vs. FDA-AERS and WHO spontaneous reporting databases

	EU-ADR		FDA-AERS		WHO	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
<b>ALI</b>	4/5=80%	5/5=100%	5/5=100%	4/4=100%	4/5=80%	2/2=100%
<b>AMI</b>	1/5=20%	5/5=100%	3/5=60%	4/4=100%	3/5=60%	3/3=100%
<b>ARF</b>	3/5=60%	3/5=60%	4/5=80%	4/5=80%	4/5=80%	4/4=100%
<b>AS</b>	1/5=20%	5/5=100%	2/5=40%	5/5=100%	2/5=40%	5/5=100%
<b>BE</b>	4/5=80%	5/5=100%	5/5=100%	5/5=100%	5/5=100%	5/5=100%
<b>CVF</b>	-	5/5=100%	-	5/5=100%	-	5/5=100%
<b>NEUTROP</b>	3/5=60%	5/5=100%	2/5=40%	5/5=100%	3/5=60%	5/5=100%
<b>PANCYT</b>	1/5=20%	5/5=100%	5/5=100%	5/5=100%	4/5=80%	5/5=100%
<b>RHABD</b>	2/4=50%	5/5=100%	4/4=100%	4/4=100%	4/4=100%	3/3=100%
<b>UGIB</b>	4/5=80%	5/5=100%	4/5=80%	5/5=100%	5/5=100%	5/5=100%
<b>Not assessable*</b>				1=AMI, 1=Rhabd		3=ALI; 2=AMI; 1=ARF; 2=Rhabd
<b>Total</b>	<b>23/44=52.3%</b>	<b>48/50=96%</b>	<b>34/39=77%</b>	<b>46/47=98%</b>	<b>34/44=77.3%</b>	<b>42/42=100%</b>

\*The non-assessable drug-event associations have not been considered in the denominator for the sensitivity and specificity calculation

**Legend:** **Sensitivity** = number of true positives/(number of true positives + number of false negatives), **Specificity** = (number of true negatives/number of true negatives + number of false positives)

Table 8: Comparison of sensitivity and specificity EU-ADR systems, FDA's AERS (replaced by FAERS in 2012) and the WHO Spontaneous reporting database. Source: Gianluca Trifirò (74)

## Annex E: FDA's "Section 921 Postings" of Potential Signals of Serious Risk

Potential Signals of Serious Risks/ New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS) in 2014 and published on the FDA Website (80):

### January-March 2014

Product Name: Active Ingredient (Trade) or Product Class	Potential Signal of a Serious Risk / New Safety Information	Additional Information (as of May 1, 2014)
Brentuximab vedotin (Adcetris)	Hepatotoxicity	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Testosterone products	Potential for drug abuse, misuse, or dependence	FDA is continuing to evaluate these issues to determine the need for any regulatory action.
Antidepressant products (except monoamine oxidase inhibitors (MAOIs))	Angle-Closure Glaucoma	FDA is continuing to evaluate this issue to determine if the current labeling for antidepressant products includes accurate information about the risk of glaucoma.

**April-June 2014**

Product Name: Active Ingredient (Trade) or Product Class	Potential Signal of a Serious Risk / New Safety Information	Additional Information (as of July 1, 2014)
Everolimus (Zortress)	Pulmonary hypertension; Pulmonary arterial hypertension	FDA is continuing to evaluate this issue to determine the need for any regulatory action.

**July-September 2014**

Product Name: Active Ingredient (Trade) or Product Class	Potential Signal of a Serious Risk / New Safety Information	Additional Information (as of October 1, 2014)
Xenazine (Tetrabenazine)	Death	FDA decided that no action is necessary at this time based on available information.
Regadenoson (Lexiscan)	Seizures, worsening or recurrence of seizures after use of aminophylline, cerebrovascular accident, and atrial fibrillation/atrial flutter	<p>The Warnings and Precautions section of the labeling for Lexiscan was updated in September 2014 to include:</p> <ul style="list-style-type: none"> <li>• seizure</li> <li>• warning not to use aminophylline in patients who have seizures after receiving regadenoson</li> <li>• cerebrovascular accident</li> <li>• atrial fibrillation/atrial flutter</li> </ul>

**October-December 2014**

Product Name: Active Ingredient (Trade) or Product Class	Potential Signal of a Serious Risk / New Safety Information	Additional Information (as of October 1, 2014)
No new safety information to report at this time.		

Table 9: FDA's "Section 921 Postings" of Potential Signals of Serious Risk (January – December 2014). **Source:** FDA (80)

## **Annex F: Participation of EU, Japan and USA in WHO PIDM**

The WHO PIDM counts 122 official members in September 2015. (99) In the following, the European countries, Japan and USA including the respective year of joining are listed:

- Austria 1991
- Belgium 1977
- Bulgaria 1975
- Croatia 1992
- Cyprus 2000
- Czech Republic 1992
- Denmark 1971
- Estonia 1998
- Finland 1974
- France 1986
- Germany 1968\*
- Greece 1990
- Hungary 1990
- Iceland 1990
- Ireland 1968\*
- Italy 1975
- Japan 1972
- Latvia 2002
- Lithuania 2005
- Malta 2004
- Netherlands 1968\*
- Norway 1971
- Poland 1972
- Portugal 1993
- Romania 1976
- Slovakia 1993
- Slovenia 2010
- Spain 1984
- Sweden 1968\*
- United Kingdom 1968\*
- U.S.A. 1968\*

\* Countries that belong to the ten founding countries of the programme.

**Source:** Uppsala Monitoring Centre (99)

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## **Eidesstattliche Versicherung**

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Troisdorf, den 01.12.2015

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Natalie Maria Welter