

# **COMPARISON OF PHARMACOVIGILANCE IN GERMANY AND JAPAN**

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## **ABSTRACT**

The most important international organisation for harmonising pharmaceutical requirements is the “International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use” (ICH). The European Union (EU) and Japan are both founding members of ICH. However, although considerable work has been completed in other areas, there has been little harmonisation of pharmacovigilance requirements through ICH. The EU and Japan have developed their own PV guidelines. Germany, an EU Member State, has supplementary requirements in addition to EU requirements.

Japan and Germany are the 3rd and 4th largest pharmaceutical markets in the world, and are highly attractive to potential marketing authorisation holders. However, finding information and understanding the legal and operative framework of pharmacovigilance aspects can be difficult for non-German and non-Japanese speaking pharmaceutical professionals.

This dissertation gives an overview of the international pharmacovigilance frameworks and the history and current approach to pharmacovigilance in Germany and Japan. It explains and compares the main laws, the competent ministries/authorities, the relevant corporate structures and main activities in the pharmacovigilance lifecycle for each country. The activities covered in this dissertation start with the submission of the product information and the risk management plan as part of the marketing authorisation application and then continue through the life-cycle of the medicinal product. Reference to English versions of information is made whenever possible.

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## TABLE OF ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AMG	Arzneimittelgesetz/ Medicinal Products Act
AMWHV	Arzneimittel- und Wirkstoffherstellungs Verordnung/ Ordinance for the Manufacture of Medicinal Products and Active Pharmaceutical Ingredients
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte/Federal Institute for Drugs and Medical Devices
BMG	Bundesministerium für Gesundheit/ Federal Ministry of Health
BPI	Bundesverband der Pharmazeutischen Industrie/ German Pharmaceutical Industry Association
CA	Competent Authority
DHPC	Direct Healthcare Professional Communication
EEA	European Economic Area
ELD	Evaluation and Licensing Division (part of PFSB)
EMA	European Medicines Agency
EPPV	Early Post-Marketing Phase Vigilance
EU	European Union
EURD	European Union Reference Dates
FAQ	Frequently Asked Question
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
GPSP	Good Post-marketing Study Practice
GVP	Good Vigilance Practice (Japan) / Good Pharmacovigilance Practice (Europe)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Study Report

Table of Abbreviations and Acronyms

IME	Important Medical Event
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MP	Medicinal Product
MR	Medical Representative
OSI /OSII	Office of Safety I/II (part of PMDA)
OTC	Over the Counter medicinal product
PAFSC	Pharmaceuticals and Food Sanitation Council
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PEI	Paul Ehrlich Institut/Paul Ehrlich Institute
PFSB	Pharmaceutical and Food Safety Bureau (MHLW)
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
QRD	Quality Review of Documents (EU Templates)
RMP	Risk Management Plan
SD	Safety Division (part of PFSB)
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
WHO	World Health Organisation

# 1 INTRODUCTION

Pharmacovigilance (PV) is defined by the World Health Organization (WHO) as the “*science and activities relating the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.*” The desirability for a scientific approach to PV was identified as early as 1968 when the WHO World Assembly called for “*a systematic collection of information on serious adverse drug reaction during the development and particularly after medicines have been made available for public use*” in resolution 16.36 (Ref 1).

The WHO emphasis on PV activities after a medicinal product (MP) has been placed on the market reflects the lack of knowledge about the MP at time of authorisation. The safety profile during marketing authorisation review is always incomplete, as it is based upon limited clinical experience in a small number of carefully selected patients, monitored extensively during studies in which they were exposed to the product for only a short amount of time. Post-authorisation PV is an ongoing process to update and refine the safety profile by providing information on the MP when used in a real-life setting.

The most important international organisation for harmonising pharmaceutical requirements is the “International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use” (ICH). The European Union (EU) and Japan are both founding members. However, although considerable work has been completed in other areas, there has been little harmonisation of PV requirements through ICH. The European Union (EU) and Japan have developed their own PV guidelines. Germany, an EU Member State, has supplementary requirements in addition to EU requirements.

Japan and Germany are the 3rd and 4th largest pharmaceutical markets in the world with turnovers worth US\$ 81,359 and US\$ 42,621 million respectively in 2015 (Ref 2). These markets are highly attractive to potential marketing authorisation holders (MAHs), but understanding the legal and operative framework and finding information regarding PV aspects can be difficult due to language barriers.

It is the aim of this dissertation to assist non-German and non-Japanese speaking pharmaceutical professionals who need to understand the PV environment in Germany and Japan. This dissertation gives an overview of the international PV frameworks and the history and current approach to PV in Germany and Japan. It explains and compares the main laws, the competent ministries/authorities, the relevant corporate structures and main activities in the PV lifecycle for each country. The PV activities covered in this

dissertation start are shown schematically in Figure 1. Activities start with the submission of the product information and the risk management plan (RMP) as part of the marketing authorisation application (MAA) and then continue throughout the life-cycle of the MP, they include handling of individual case study reports (ICSRs) and submission of periodic safety update reports (PSURs).

Reference is given to English versions of information whenever possible.

It should be noted that this thesis uses the European terms “medicinal product” and “post-authorisation” for those sections on Germany/Europe and the corresponding terms “drug” and “post-marketing” for sections on Japan, the US and ICH. The focus is on chemical entities. Biologics are subject to stricter pharmacovigilance requirements which will not be explained in this work.

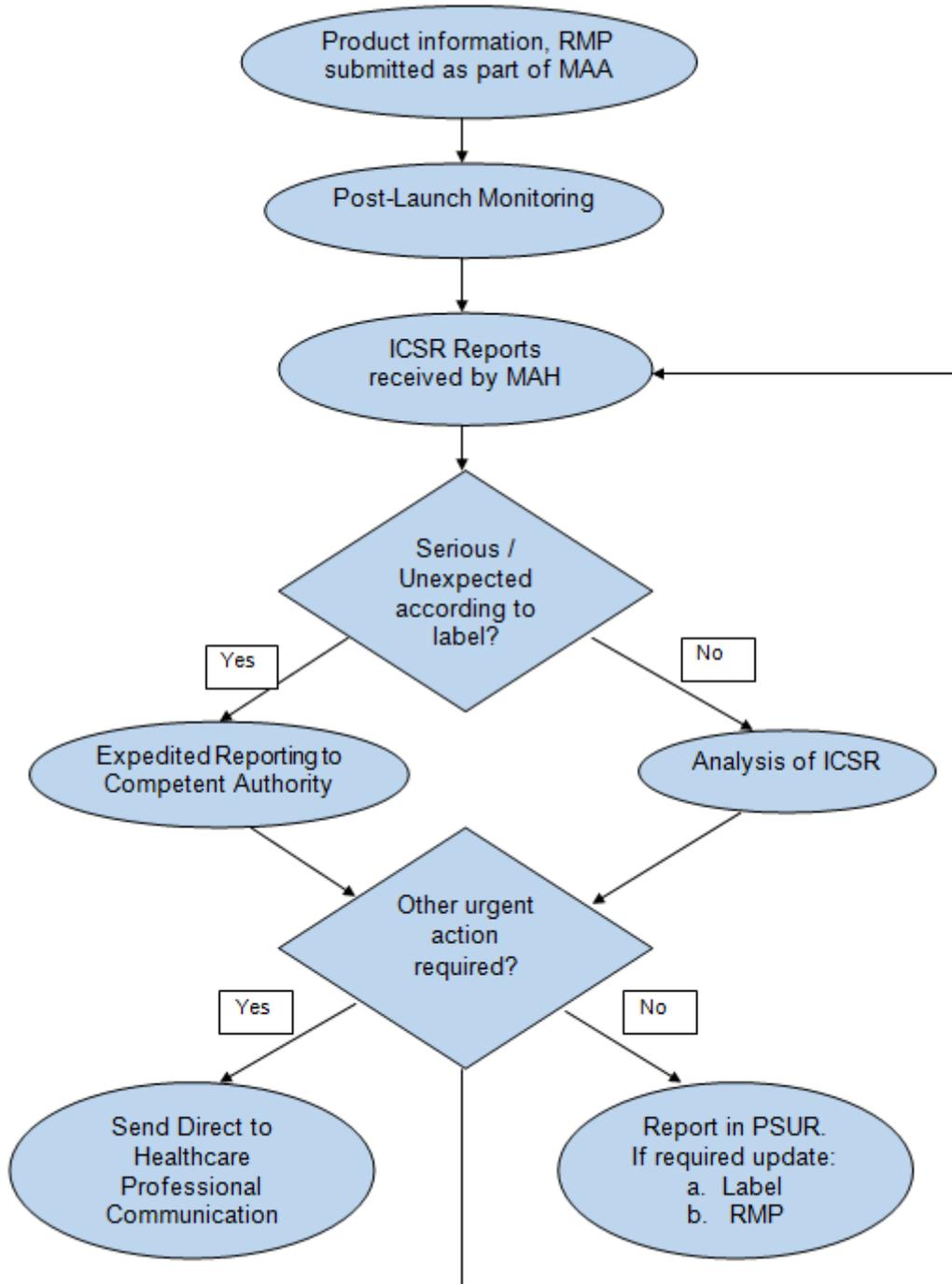


Figure 1 Flowchart of Pharmacovigilance activities addressed in this work

## **2 THE INTERNATIONAL PV FRAMEWORK: ICH AND EU**

### **2.1 The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use**

Both Germany (as an EU member state) and Japan are founding members of “The International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use” (ICH, the name changed from “Conference” to “Council” in 2015). ICH was set up in 1990 with the aim of harmonising regulations between the three major pharmaceutical markets of Europe, the U.S. and Japan. Harmonising regulations allows data generated in accordance with ICH regulations in one region to be accepted by another region, which reduces cost and time in bringing MPs to market (Ref 3). The ICH produces quality, safety, efficacy and multidisciplinary guidelines which are made mandatory in the ICH member countries and regions by being incorporated into local law. The ICH guidelines covering PV are found in the efficacy (E) and multidisciplinary (M) guidelines. However, with the exception of E2B, which is a technical guideline for harmonizing data elements and specifications, the guidelines are relatively short and are also quite old, particularly E2D and E2E. The shortness and age of the guidelines show that there has been only limited harmonisation on PV aspects in the ICH regions (Table 1).

Table 1 ICH Post-Authorisation PV Guidelines, Lengths &amp; When Adopted

ICH Guidance and Revision No.	Title	Length (pages)	Year adopted; EU, Japan
E2B (R3)	Clinical Safety Data Elements for Transmission of Individual Case Safety Reports	134	2013
E2C (R2)	Periodic Benefit-Risk Evaluation Report	37	2012
E2D	Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting	11	2003 (EU) 2005 (Japan)
E2E	Pharmacovigilance Planning	16	2004 (EU) 2005 (Japan)
M1	MedDRA Terminology Medical Dictionary for Regulatory Activities	N/A	

The E2B, E2D and M1 guidelines harmonise requirements for safety reporting timelines and terminology. The data elements in E2B that must be transmitted for ICSRs in Japan and Europe have been extensively covered by another work and will only be touched upon briefly in this thesis (Ref 4).

To facilitate harmonisation, the E2D guideline defines certain terms used throughout the ICH regions, including key definitions as follows (Ref 5):

- adverse events (AEs), which include all untoward occurrences in patient given a pharmaceutical product
- adverse drug reactions (ADRs), which include only those AEs where a causal relationship cannot be ruled out
- the seriousness of the event; an event is classed as serious if at any dose it:
  - *“results in death*
  - *is life-threatening*
  - *requires inpatient hospitalisation or prolongation of existing hospitalisation*
  - *results in persistent or significant disability/incapacity*
  - *is a congenital anomaly/birth defect*
  - *is a medically important event or reaction”* (ICH E2D 2.3 “*Serious AE/ADR*”)

- The expectedness of an event; an event is “unexpected” if it is not listed in the ADRs specified in the package insert and Summary of Product Characteristics (SmPC) or if it occurs in a more specific or more severe manner or at a greater frequency.

The definitions of “serious” and “expected” are of vital importance in deciding whether an event is subject to expedited reporting or not.

The E2C guideline harmonises requirements for regular submission of safety data, known in Europe as the Periodic Safety Update Report (PSUR).

The E2E Guideline is of special interest as it introduces the concept of a life-cycle approach to PV. The life-cycle starts with the submission of a safety specification and PV plan at the time of applying for marketing authorisation and proceeds with ongoing post-authorisation PV activities to enable a continual refinement of the benefit-risk profile of the MP. In accordance with this guideline MAHs must commit to providing the following (Ref 6):

- *“Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;*
- *The preparation of reports for regulatory authorities:*
  - *Expedited adverse drug reaction (ADR) reports;*
  - *Periodic Safety Update Reports (PSURs).*
- *Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities;*
- *Other requirements, as defined by local regulations.”* (ICH Guideline E2E Pharmacovigilance Planning, Section 3.1.2 “*Routine Pharmacovigilance Practices*”)

The first bullet point requires that MAHs have systems and processes in place, but does not specify whether these systems and processes must be disclosed to competent authorities – that is a matter for individual ICH member states to decide. From the last bullet point, the ICH requirements may be considered as minimum requirements and individual member states may set higher requirements under the guise of “local regulations”. The EU has made use of this freedom and has, over the last seven years, developed a much more comprehensive set of PV requirements.

## 2.2 European Union

In December 2010 the European Parliament signed Directive 2010/84/EU and Regulation (EU) Number 1235/2010 to strengthen the PV requirements of the key European laws governing authorisation and supervision of medicinal products (Directive 2001/83/EC and Regulation (EC) 726/2004). In 2012 further legislation was adopted to introduce a new scheme to make public medicinal products subject to additional monitoring and to place requirement on MAHs to notify the competent authority of reasons for withdrawing medicinal products from the market (Regulation (EU) Number 1027/2012 and Directive 2012/26/EU (Ref 7)). Building on the legislation, the European Union has developed a very comprehensive set of requirements for pharmacovigilance, known as the Good Pharmacovigilance Practice (GVP) Modules (Ref 8), listed as follows (Table 2):

Table 2 EU Good Pharmacovigilance Modules and Lengths

<b>GVP Module No.</b>	<b>Title</b>	<b>Length (pages)</b>	<b>Year published</b>
Module I	Pharmacovigilance systems and their quality systems	25	2012
Module II	Pharmacovigilance system master file	20	2012
Module III	Pharmacovigilance inspections	19	2012
Module IV	Pharmacovigilance audits	12	2015
Module V	Risk management systems	60	2012
Module VI	Management and reporting of adverse reactions to medicinal products	90	2012
Module VII	Periodic safety update report	68	2012
Module VIII	Post-authorisation safety studies	27	2012
Module IX	Signal management	17	2012
Module X	Additional monitoring	9	2013
Module XV	Safety communication	15	2013
Module XVI	Risk minimisation measures – selection of tools and effectiveness indicators	22	2014

Comparing these modules to the ICH guidelines reveals that the EU modules, which apply to all MPs placed on the EU market regardless of the authorisation route, are newer and more comprehensive. In addition to the modules listed, there are product specific guidelines for vaccines / biological medicinal products, population specific guidelines for pregnant women & children and templates for Direct Healthcare Professional Communications (DHPCs).

EU law also allows for additional local requirements to be made by Member States. National requirements specific to Germany are explained in this work.

### **3 PHARMACOVIGILANCE IN GERMANY: OVERVIEW**

#### **History**

The main event creating the public demand and political will to strengthen PV in Germany was the Contergan tragedy. Contergan was a sleeping pill manufactured by the German company Grünenthal and was available as an over-the-counter medicine in the late 1950's. It was also recommended by doctors to expectant mothers to combat morning sickness due to the sedative effects of its active ingredient thalidomide, which is the name by which it is widely known in non-German speaking countries. Thalidomide affected foetal development and led to babies being born with severe limb, eye, heart, alimentary and urinary tract deformations as well as blindness and deafness (Ref 9). Around 5,000 babies were born in the former West Germany with deformities caused by thalidomide in the late 1950s and early 1960s (Ref 10). The tragedy resulted in far-reaching changes. Testing of pharmaceuticals was made compulsory for the first time in 1964 in West Germany; the Institute for Pharmaceuticals (Institut für Arzneimittel; the fore-runner of the current competent authority) was formed in 1975 to review quality, efficacy and safety of pharmaceuticals and in 1976 a major overhaul of the Medicinal Products Act ("Arzneimittelgesetz", acronym AMG) came into effect.

In the 1990s a further tragedy unfolded involving HIV tainted blood products given to haemophiliacs which led to 1,846 German patients being infected with HIV and resulted in the dissolution of the Federal Health Agency in 1994 (Ref 12). Responsibilities were split between three new independent organisations; the Federal Institute for Drugs and Medical Devices (the BfArM) the Robert Koch Institute and the Federal Institute for Consumer Health Protection and Veterinary Medicines.

#### **Current Approach**

The current German PV approach is mostly harmonised within the EU and ICH framework although there are German specific requirements for company personnel and the handling of DHPCs. The European lifecycle approach, based on ICH, is followed and the safety of an MP is assessed continuously throughout the life of the product (Figure 2).

Responsibility for PV is shared between MAHs and competent authorities (CAs); healthcare professionals are requested to assist by reporting AEs but have not legal obligations to report. The PV obligations of the MAH are the same for prescription, pharmacy only or over-the-counter (OTC) medicines. CAs are empowered to enforce these obligations through the MAA, renewal and variations procedures and via

inspections. Sensitivity towards MP use in pregnancy is a subject still relevant in Germany and in the EU, as reflected in the “Guideline on exposure to medicinal products during pregnancy: need for post-authorisation data” which requires that MAHs carry out active surveillance to collect post-authorisation safety data on use of a medicinal product in pregnancies (Ref 12). CAs do not distribute relief funds for patients who have suffered ADRs.

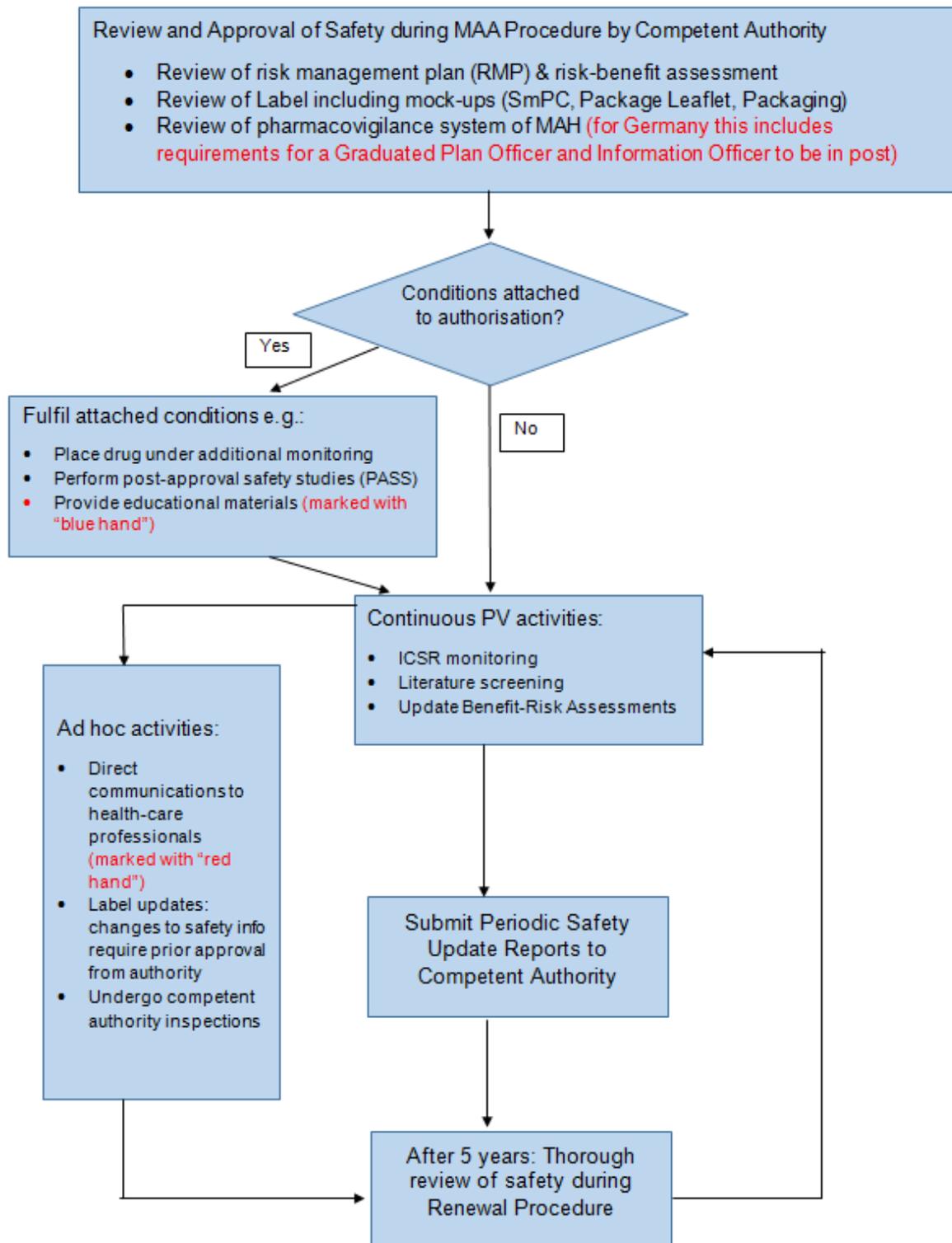


Figure 2 Lifecycle Approach to Pharmacovigilance in Germany/EU (unique requirements for Germany compared to rest of EU shown in red)

## **4 PHARMACOVIGILANCE IN JAPAN: OVERVIEW**

### **History**

There are two particular tragedies that rocked Japan and forced the government to tighten regulation of PV in the pharmaceutical industry.

The first and most important was the use of Hepatitis C infected blood products between 1971 and 1990, which resulted in at least 10,000 patients being infected with Hepatitis C. Most affected were pregnant women who received blood-derived coagulant products to stop haemorrhaging after childbirth. These products continued to be used in Japan long after their withdrawal in the US in 1977. Japanese health authorities knew the names of 418 patients who were unknowingly infected with hepatitis, but did not inform these patients of their condition. After a group of patients sued the government and pharmaceutical companies, a law was passed in 2008 granting compensation to those affected (Ref 13). A special committee was set up (the “Committee to verify the pharmaceutical administration for investigation into the hepatitis C infection incident and prevention of recurrence”) to investigate what went wrong and in 2010 issued a final report which criticised pharmaceutical administration in Japan and included a wide range of recommendations to prevent such a situation happening again, including recommendations on adverse event reporting and PV programmes (Ref 14).

The second tragedy was the use of HIV infected blood products for haemophiliacs in the 1990s. Until 1999, 1,434 patients were infected with HIV due to contaminated blood products, of whom 631 died (Ref 15). The scandal was the decision to use unheated blood products even though it was known that these could be HIV-tainted. Patients and families successfully sued the Japanese Ministry of Health and Welfare (MHLW) and five pharmaceutical manufacturers. In 1996 the MHLW set up a special “Relief Program for Patients of Aids Caused by Blood Products” and introduced an advanced evaluation system in 1998 to shorten the period for approved US AIDS products to be approved in Japan (Ref 16).

### **Current Approach**

The current Japanese PV approach is harmonised with ICH requirements, but has certain differences to the European system. Whereas in Europe each newly marketed product goes through the renewal procedure after 5 years, in Japan each newly marketed product goes through the re-examination procedure at 8-10 years and then re-evaluation on an ad-hoc basis (Figure 3). Commitments to post-marketing studies and surveillance are

made at the time of approval and these must be conducted to the standards of Good Post-Marketing Study Practice (GPSP) a set of standards unique to Japan.

Responsibility for PV is placed on MAHs, the Ministry, the regulatory agency (the Pharmaceuticals and Medical Devices Agency, acronym PMDA), healthcare professionals and even ordinary citizens. The PV obligations of the MAH differ depending on whether the drugs marketed by the company are prescription drugs or not. There remains a strong focus on infections in safety reporting. The regulatory agency makes recommendations but the final decisions for MAAs, re-examinations and re-evaluations are taken by the Ministry. The agency does not perform PV inspections. The agency distributes relief funds to patients who have suffered ADRs.

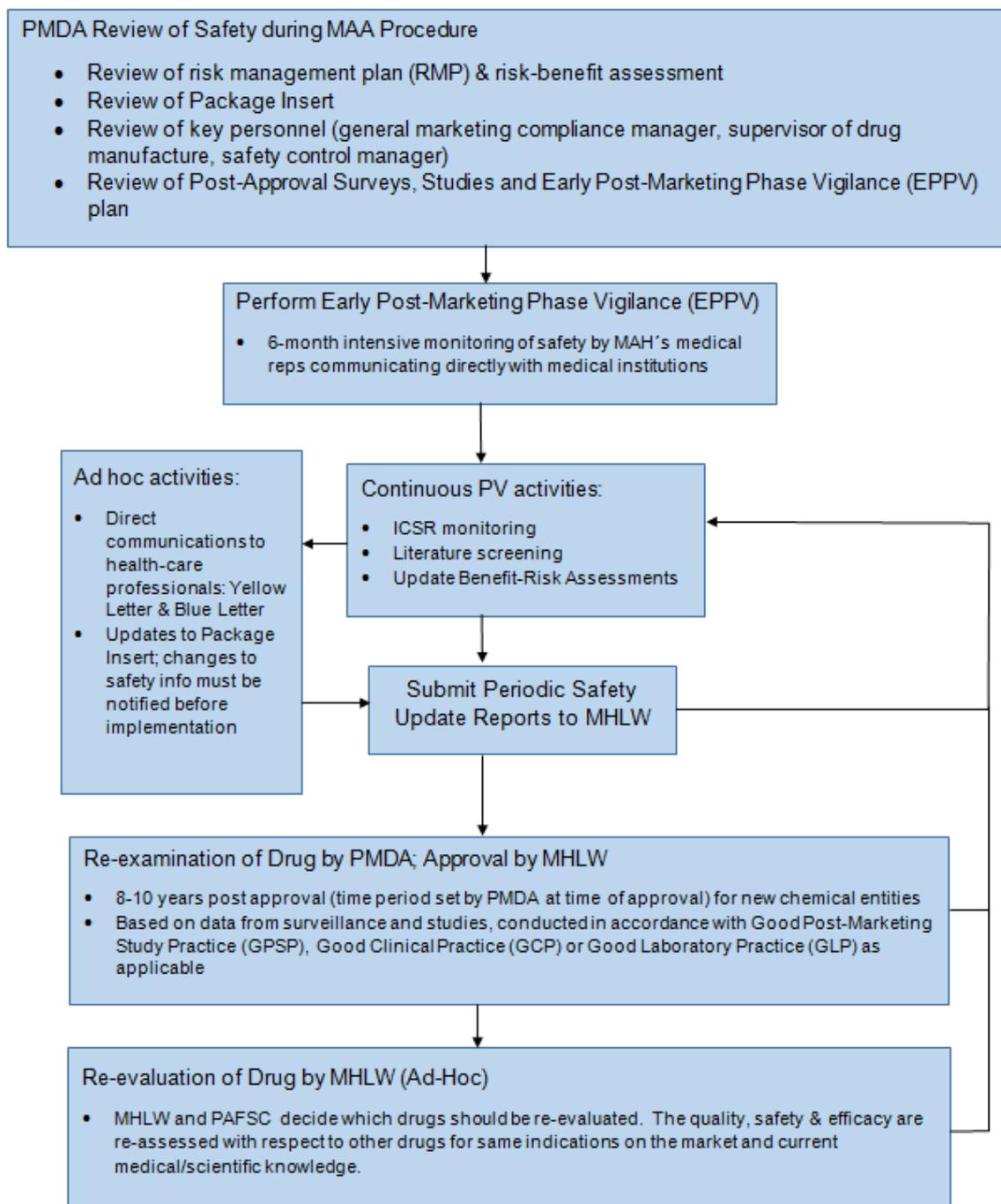


Figure 3 Lifecycle Approach to Pharmacovigilance in Japan

## 5 LEGAL FRAMEWORK FOR PHARMACOVIGILANCE

This section considers and compares the main laws, ordinances and regulations that govern PV in Germany and Japan. In particular the following questions are answered:

- What are the main laws and ordinances governing pharmacovigilance?
- Who are the addressees of these laws?
- Are these laws and regulations available in English?

### 5.1 The Legal Framework in Germany

The legal framework governing pharmacovigilance in Germany consists of one main law and one main ordinance but in addition there are announcements (“Bekanntmachungen”), explanatory notes (“Erläuterungen”) and Frequently Asked Questions (FAQs) published by the higher federal competent authorities. Announcements give further details on competent authorities’ requirements, may have a legal status, depending on the content and should be followed by MAHs. Explanatory notes do not have a legal status but are designed to help MAHs understand particular processes. FAQs are important as they contain the interpretations by the competent authorities of legal and regulatory issues.

#### **What are the main laws and ordinances affecting pharmacovigilance?**

The main **law** governing medicinal products is the Arzneimittelgesetz (the Medicinal Products Act; acronym AMG). This law dates from 1961 and has been subject to various amending Acts since then; the latest amendment entered into force on 24<sup>th</sup> December 2016. The law incorporates major European Directives, including those most relevant for pharmacovigilance:

- Directive 2001/83/EC (the Community code relating to medicinal products for human use)
- Directive 2010/84/EU (amending Directive 2001/83/EC as regards pharmacovigilance)
- Directive 2012/26/EU (amending Directive 2001/83/EC as regards pharmacovigilance)

The AMG covers medicinal products for humans and animals.

The main **ordinance** with relevance to pharmacovigilance is the Ordinance for the Manufacture of Medicinal Products and Active Pharmaceutical Ingredients (“Arzneimittel- und Wirkstoffherstellungsverordnung”, acronym AMWHV). This ordinance incorporates

the good manufacturing practice (GMP) requirements of 2003/94/EC, and is relevant to pharmacovigilance because of the requirements it contains regarding the German pharmacovigilance MAH's "Stufenplanbeauftragter" (Graduated Plan Officer), details of which will be explained later.

### **Who are the addressees of these laws?**

The main addressees of the AMG are marketing authorisation holders and the two higher federal competent authorities, the Federal Institute for Drugs and Medical Devices ("Bundesinstitut für Arzneimittel und Medizinprodukte", acronym BfArM) and the Paul Ehrlich Institute (acronym PEI).

### **Are any of these laws available in English?**

English translations of several MP-related laws are available for the non-German speaking public on the Federal Ministry of Health's website under the link [Laws in English](#). An English version of the slightly out-of-date 2014 AMG is available on the website under the link [Medicinal Products Act](#) (Ref 17). The website emphasises that these translations are "*intended solely as a convenience to the non-German reading public*" and therefore contains no guarantee of their accuracy; nevertheless they will be of help to all those interested in finding out more about German pharmaceutical legislation. Unfortunately, there is currently no English version of the AMWHV Ordinance available.

## **5.2 The Legal Framework in Japan**

The legal framework governing medicinal products in Japan is made up of one main law, supported by a cabinet ordinance, a ministerial regulation, ministerial ordinances and numerous notifications (Figure 4).

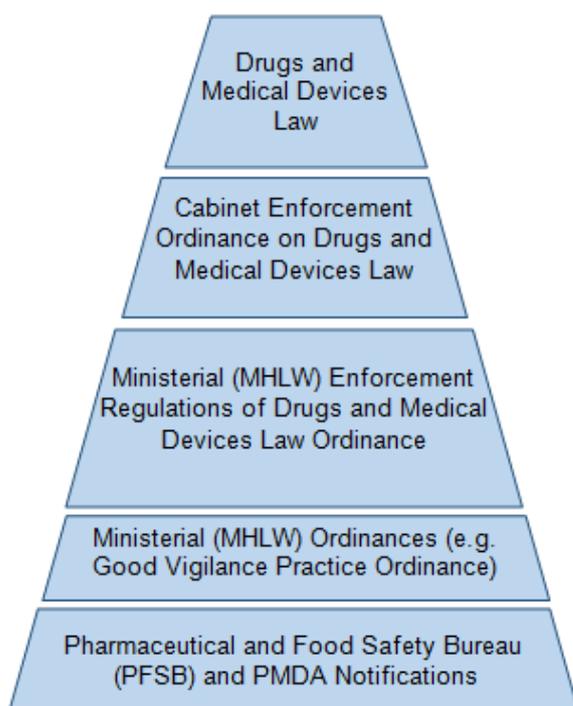


Figure 4 Relationship between Japanese law, cabinet ordinance, ministerial regulation, ministerial ordinances and notifications

Notifications are issued by the Pharmaceutical and Food Safety Bureau (PFSB) of the MHLW, from either the Safety Division (SD) or the Evaluation and Licensing Division (ELD) and from the Office of Safety I (OSI) and Office of Safety II (OSII) of the PMDA. Notifications are identified through acronyms and numbers (Table 3)

Table 3 Notification ID and Sources

Notification ID	Notification Source
PFSB/SD 0001	Pharmaceutical and Food Safety Bureau: Safety Division
PFSB/ELD 0001	Pharmaceutical and Food Safety Bureau: Evaluation and Licensing Division
PMDA/OSI 0001	Pharmaceuticals and Medical Devices Agency: Office of Safety I
PMDA/OSII 0001	Pharmaceuticals and Medical Devices Agency: Office of Safety II

Some notifications are issued jointly and have a double numbering system.

### **What are the main laws and ordinances relevant to pharmacovigilance?**

The main Japanese law governing medicinal products and medical devices is the “Law on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products and Cosmetics” (shortened to the “Drugs and Medical Devices Law”) which was implemented in November 2015 (Ref 18). This law is a re-working of the previous “Pharmaceutical Affairs Law” which was first enacted in 1943, and revised/partially amended seven times before the latest partial amendment promulgated in November 2013 changed the name of the law to the “Drugs and Medical Devices Law” (Ref 19).

The Drugs and Medical Devices Law needs to be read in conjunction with the Enforcement Ordinance and the Enforcement Regulations of this Law. For example, Article 18 paragraph 3 of the Law states that MAHs may contract out those aspects of post-marketing safety work specified by MHLW ordinance, and article 97 and article 98 of the Regulations specify which activities may be subcontracted and secondarily subcontracted. The Drugs and Medical Devices Law does not incorporate ICH guidelines, these are adopted through PFSB Notifications.

The most important Ordinance governing pharmacovigilance is the “Ministerial Ordinance on Good Vigilance Practice for drugs, quasi-drugs, cosmetics and medical devices (MHLW Ministerial Ordinance No. 135 of 2004, known as the “GVP Ordinance”, last amended in 2014 (Ref 20)). The second most important ordinance is the “Ministerial Ordinance on Good Post-Marketing Study Practice for Drugs” (MHLW Ministerial Ordinance No. 171 of 2004)

### **Who are the addressees of these laws?**

As we would expect the Drugs and Medical Devices Law is addressed clearly to marketing authorisation holders as well as to government ministry of the MHLW and the PMDA. Other official organisations such as the Pharmaceutical Affairs and Food Sanitation Council (e.g. in article 42) are also addressed. However, one unique aspect of pharmacovigilance in Japan is that responsibilities are also directed at healthcare professionals and even at ordinary citizens. The General Provisions of Chapter 1 of the Drugs and Medical Devices Law make very interesting reading in particular Articles 1-5 and 1-6:

- ***“Healthcare professionals such as physicians, dentist, pharmacists and veterinarians must deepen their knowledge and understanding of the efficacy and safety of drugs etc and proper use thereof, and provide persons who use drugs***

*(...) and persons who intend to purchase or obtain drugs, etc. with the correct and appropriate information of matters relating to the proper use thereof.*” (Article 1-5; underlining and emphasis by author)

- *“**Citizens** must properly use drugs, etc. and deepen their knowledge and understanding of the efficacy and safety thereof.”* (Article 1-6 emphasis by author)

This makes reading of package leaflets and SmPCs almost compulsory for both HCPs and patients and places requirements on ordinary citizens to comply with prescribing instructions.

A legal obligation is also placed on a wide variety of proprietors and healthcare professionals to report certain types of adverse drug reaction as stated in Article 68-10:

- *“When proprietors of pharmacies, hospitals, clinics or veterinary clinics, or physicians, dentists, pharmacists, registered sellers, veterinarians or other healthcare professionals learn of cases of diseases, disabilities or deaths suspected to be caused by adverse drug reactions or other reasons related to drugs, medical devices of regenerative medicine products, or infectious diseases suspected of being caused by the use of such products, and they confirm that it is necessary to prevent the onset or spread of hazards to public health or hygiene, they must report this fact to the Minister.”* (Article 68-10; underlining by author)

### **Are any of these laws/ordinances/regulations available in English?**

A free translation of the Drugs and Medical Devices Law, enforcement ordinance and enforcement regulations is offered by the Japanese Law Translation Database, under the auspices of the Japanese Ministry of Justice, but the website emphasises that these are unofficial translations ([Japanese Drugs and Medical Devices Law in English](#)) ([Enforcement Ordinance](#)) ([Enforcement Regulations](#)). The publishing house “Jihou” which specializes in pharmaceutical publishing offers a bilingual edition of the drugs and devices law, enforcement ordinance and enforcement regulations in book form (Ref 21). The regulatory intelligence company Cortellis provides English translations of Japanese laws, ordinances and regulations as part of their services.

The PMDA in its section [Regulatory Information](#) (Ref 22) offers some English translations of Japanese Ministerial Ordinances & notifications, and some translations of safety related notifications & administrative notices are available in the section [Post-marketing Safety Measures Regulatory Information](#) (Ref 23).

### **5.3 Comparative Summary of Legal PV Framework**

Both Germany and Japan have one main pharmaceutical law underpinned by ordinances and notifications. The main German law is the AMG which covers only medicinal products, but for both humans and animals. The AMG incorporates ICH and EU principles and requirements and is addressed to MAHs and competent authorities. PV requirements are the same for all types of MPs (prescription, pharmacy only and over-the-counter products). Notifications and explanations on how to interpret the law come from the two higher federal competent authorities; BfArM and PEI. The AMG is available in English but the AMWHV ordinance covering specific duties of the Graduated Plan Officer (the key person in pharmacovigilance) is not. Some notifications, explanations and FAQs are available in English.

In Japan the legal system is more complex. The main Japanese law is the Drugs and Medical Devices Law which covers both medicinal products and medical devices but only for humans. The law needs to be considered together with the cabinet enforcement ordinance and the ministerial enforcement regulations. The law is addressed to a broader audience and contains obligations for healthcare professionals and even ordinary citizens. Requirements concerning pharmacovigilance differ depending on the type of drug (prescription, non-prescription or quasi-drugs). Ministerial ordinances come from the MHLW whilst notifications come from the Pharmaceutical and Food Safety Bureau (PFSB) of the MHLW and the PMDA. ICH pharmacovigilance guidelines are adopted through PFSB Notifications. The law, enforcement ordinance and enforcement regulations are all available in English. Some notifications are available in English.

## **6 PV MINISTRIES AND AUTHORITIES**

Who makes the legislation governing PV activities and who administers the legislation? What powers lie with ministries and what powers lie with authorities? The next section provides answers to these questions by explaining and comparing the ministry and authority structures and function in Germany and Japan.

### **6.1 Ministry and Authorities in Germany**

#### **Government Ministry**

The German Federal Ministry of Health (“Bundesministerium für Gesundheit”; acronym BMG) is the ministry with overall responsibility for health in Germany, it drafts health-related policies and legislation, including the legislation which governs medicinal products and medical devices.

#### **Competent Authorities**

Under the remit of the BMG are two competent higher authorities responsible for human medicinal products and medical devices; the BfArM and the PEI.

The pharmacovigilance system of the two competent authorities is set out in article 62 of the AMG.

BfArM and PEI are independent one-stop shops, which, in the frame of nationally authorised products, cover all aspects of pharmaceutical development and licensing, starting from authorisation of clinical trials to review and approval of the marketing authorisation dossier and following up with inspections and renewal & variation approvals for those products under their remit. BfArM and PEI can impose conditions on the MAH at time of marketing such as the requirement for post-authorisation safety studies or that the MP is made subject to additional monitoring. They can also require MAHs to make changes to the safety information of the labeling, and any safety information changes proposed by an MAH must be reviewed and approved by BfArM/PEI before implementation. The range of PV-related interactions that these authorities have with MAHs and Agencies is shown in Figure 5.



Figure 5 BfArM/PEI PV-Interactions with MAHs

For products authorised by the mutual recognition procedure/decentralised procedure for which Germany is the reference member state, the BfArM and PEI have similar powers to nationally authorised products regarding inspections, variations, PSUR review etc. For centrally authorised products, BfArM and PEI work together with the European Medicines Agency (EMA) when Germany is the Rapporteur or Co-Rapporteur; PV inspections can be undertaken on behalf of EMA when the pharmacovigilance system master file of the pharmaceutical company is located in Germany.

### **Competent Authority BfArM**

The BfArM is the slightly larger of the two German competent authorities, employs roughly 1,000 staff and is located in Bonn, in the federal state of Nordrhein Westphalia (Ref 24).

The medicinal products for which BfArM is responsible is not defined with an inclusive list, instead the remit of BfArM is defined as follows:

- *“The competent higher federal authority shall be the Federal Institute for Drugs and Medical Devices unless either the Paul Ehrlich Institute (the Federal Agency for Sera and Vaccines) or the Federal Office of Consumer Protection and Food Safety is competent.”* (Article 77(1) of the AMG, (Ref 17))

The BfArM is responsible for all human medicinal products apart from biologics and advanced therapy medicinal products which are covered by the PEI. The PEI covers advanced medicinal products and biologics for humans as well as biologics for animals. The Federal Office of Consumer Protection and Food Safety is responsible for medicinal products used in animals and is no further interest in the context of this thesis.

In 2015 the BfArM dealt with over 57,000 ADRs, of which roughly 48,000 were reported by MAHs and the remaining 9,000 from other sources. A breakdown of the other sources shows that over 5,000 ADR reports came from the Drug Commissions of the German Medical Association and the German Pharmacists; just over 1,500 come from individual health care professionals (Ref 25).

### **Competent Authority PEI**

The PEI is somewhat smaller than the BfArM, employs roughly 800 staff and is located in Langen, in the federal state of Hessen (Ref 26). The remit of the Paul Ehrlich Institute is defined as follows:

*“The Paul Ehrlich Institute shall be competent for sera, vaccines, blood preparations, bone marrow preparations, tissue preparations, tissues, allergens, advanced therapy medicinal products, xenogenic medicinal products and blood components manufactured using genetic engineering”* Section 77 (2) of the AMG.

PEI received 24,700 ADR reports in the year 2014 (Ref 27).

## 6.2 Ministry and Authority in Japan

### Government Ministry

The government department responsible for medicines and medical devices is the Ministry of Health, Labour and Welfare (MHLW). The structure of the ministry is quite complex and includes various Bureaus, Councils, Affiliated Institutions and Local Branches. For pharmacovigilance purposes the most important parts are the Pharmaceutical and Food Safety Bureau (PFSB), the Pharmaceuticals and Food Sanitation Council (PAFSC) and the National Institute of Health Sciences. The organisation of the MHLW and associated institutions is shown in Figure 6.

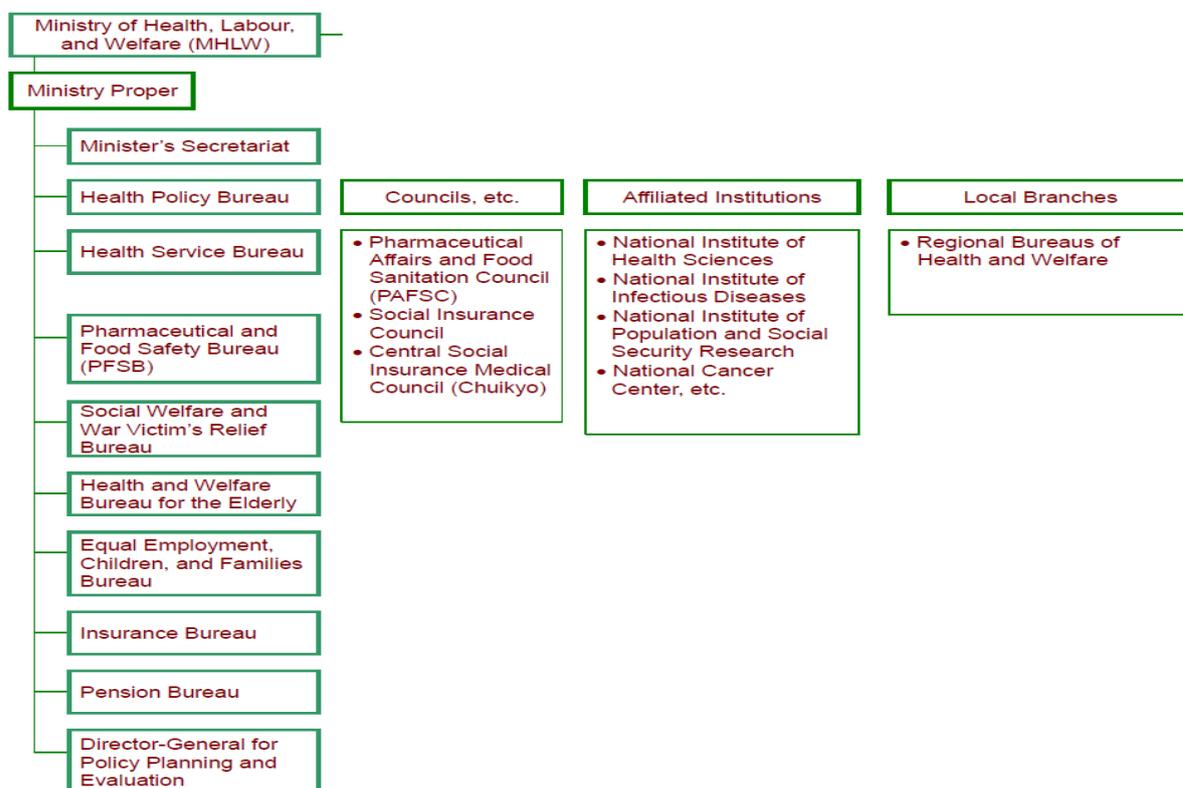


Figure 6 Organisation of MHLW and associated institutions (Excerpt from "Pharmaceutical Administration and Regulation in Japan 2015 (Ref 28))

The MHLW is responsible for granting marketing authorisations. The process is more complex than the European system. The MAA dossier is reviewed by the PMDA who

consult with external experts as necessary; the PMDA then sends their review report to the MHLW who consult with the PAFSC before making a final decision (Figure 7).

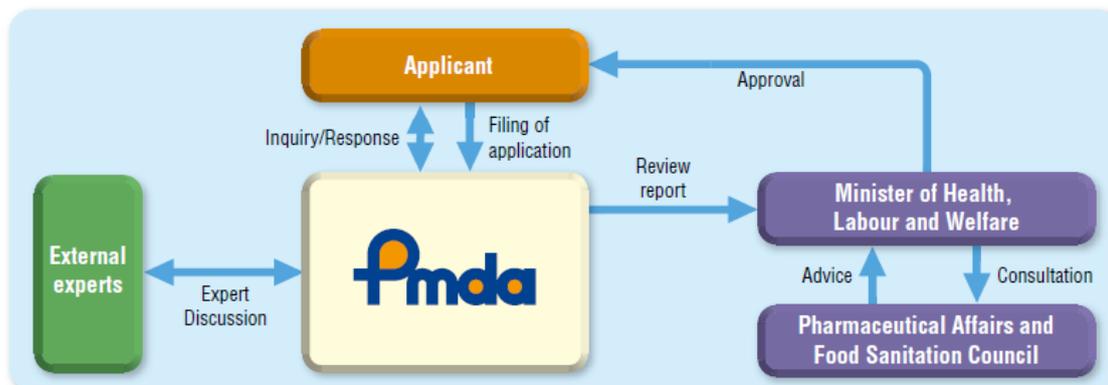


Figure 7 Review and approval process of marketing authorisation applications in Japan

### Pharmaceuticals and Medical Devices Agency PMDA

The PMDA is located in Tokyo and has 873 employees in three departments of relief, review and safety. Part of the PMDA started as a fund for the relief of patients who suffered adverse drug reactions from the hepatitis scandal of the 1970s, and then underwent various reorganisations and merged with other government bureaus until in 2004 the PMDA was established in its current form (Figure 8).

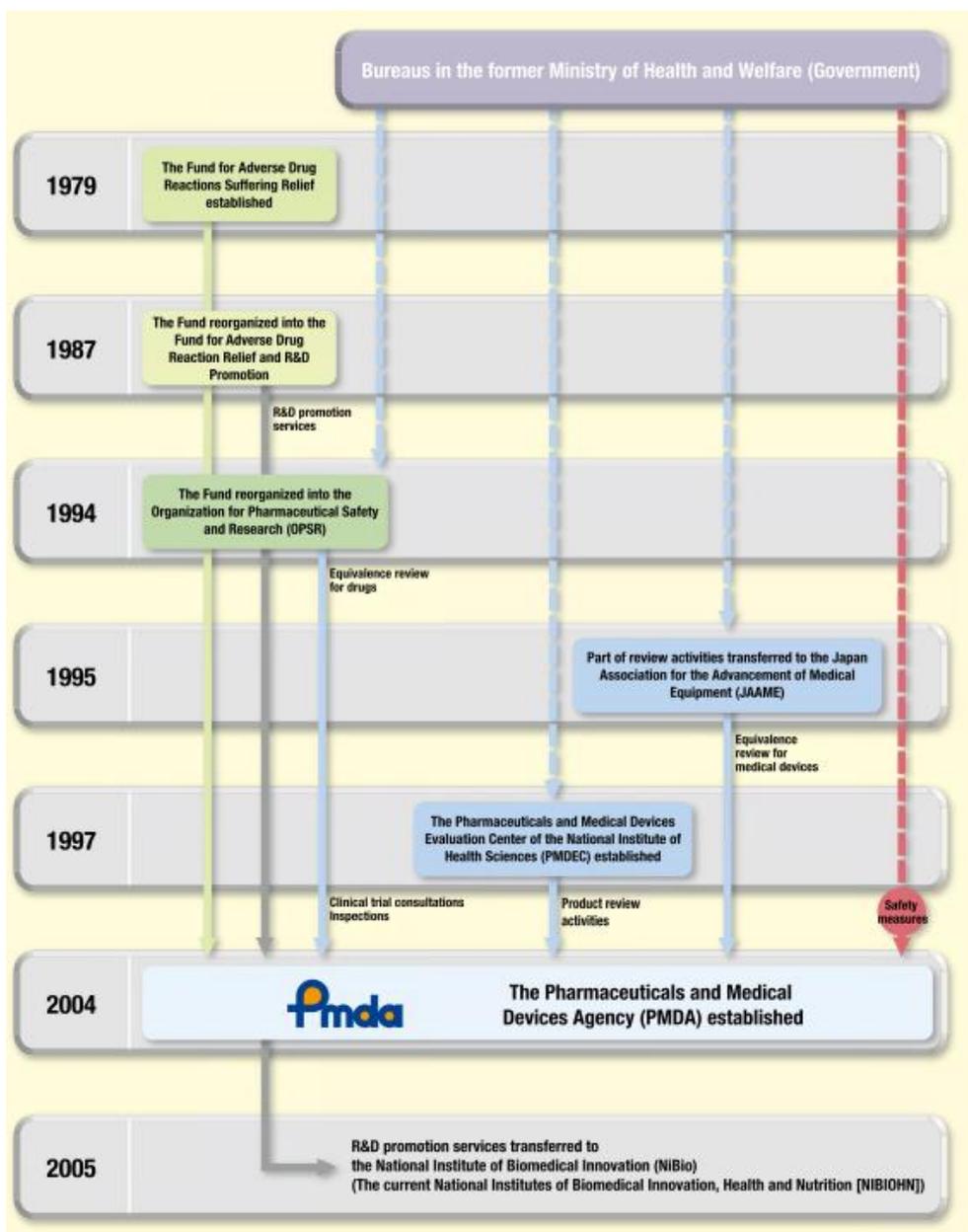


Figure 8 History of the PMDA (source PMDA (Ref 29))

The relief aspect of its work continues today and in financial year 2015, the PMDA processed over 1,500 claims for relief due to adverse drug reactions and 2 claims for infections acquired through biological products. In the same year the PMDA oversaw payments of over €17 million made to claimants (Ref 29). A total of 37 employees work in the relief department.

The review department is the largest department with 560 employees and reviews marketing authorisation applications and re-examination applications for drugs, biologics,

quasi-drugs, medical devices and diagnostics. As already stated, approvals are not granted by PMDA but by MHLW. This department carries out compliance assessments and inspections for studies carried out under Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Post-marketing Study Practice (GPSP). The review department also develops standards for the Japanese Pharmacopoeia (Ref 29).

The safety department has 185 employees, processes ADRs reported by MAHs and medical institutions, receives package inserts or revisions to precautions submitted by MAHs, provides consultation on safety issues to MAHs and provides information (package inserts, risk management plans as well as own guidances) to consumers. In 2015 the PMDA received over 51,000 ADR reports in Japan from MAHs and almost 5,000 from health care professionals.

### **6.3 Comparative Summary of Ministries and Authorities**

Both Germany and Japan have one Ministry responsible for health, the BMG in Germany and the MHLW in Japan. The BMG has a relatively simple structure and power is delegated to the two competent authorities. The MHLW by contrast has a complex structure and several different organisations are involved in drug administration; the power to grant marketing authorisations and renewals remains with MHLW.

Germany has two competent authorities, BfArM and PEI which are one-stop shops for all aspects of pharmaceutical administration including review, approvals and inspections. BfArM and PEI differ in the products that they are responsible for; BfArM is responsible for medicinal products and medical devices, but not biologics. PEI is responsible for advanced therapies and all biologics (both for human and animal use). In the context of nationally authorised products, BfArM and PEI have power to grant approvals and conduct PV inspections. For decentralised or mutual recognition procedures where Germany is the Reference Member State, the BfArM and PAI have powers to conduct PV inspections. For centrally authorised products BfArM and PEI conduct PV inspections on behalf of EMA when the pharmacovigilance system master file of the pharmaceutical company is located in Germany.

The Japanese PMDA reviews MAA dossiers and renewal dossiers but does not make the final decisions; the MHLW are responsible for this. The PMDA is not empowered to conduct PV inspections. However, the PMDA administers funds for relief of patients who have suffered ADRs, a function not known in Germany. The PMDA also offer consultation

services including a wealth of information to the public; a function not mirrored in BfArM/PEI. A comparison of the activities of BfArM, PEI and PMDA is given in Table 4.

Table 4 Comparison of BfArM, PEI and PMDA PV-Related Activities

Activity	BfArM	PEI	PMDA	Comments
Review of MAA Dossier	Yes	Yes	Yes	
Granting of Marketing Authorisation	Yes	Yes	No	In Japan MA granted by MHLW
Placing Conditions on Marketing Authorisation	Yes	Yes	No	
Conducting PV Inspections	Yes	Yes	No	In Japan PV inspections carried out by local authorities
Requiring changes to Labeling	Yes	Yes	No	In Japan changes required by MHLW
Reviewing changes to Labeling	Yes	Yes	Yes	
Receiving ADR reports	Yes	Yes	Yes	
Number of local ADR reports dealt with in 2015	57,000	24,700	56,000	
Conducting own PV research	Yes	Yes	Yes	
Engaging in international cooperation	Yes	Yes	Yes	
Reviewing Renewal Applications/Re-examinations	Yes	Yes	Yes	
Granting Renewals/Re-examinations	Yes	Yes	No	
Provision of information for the public	No	No	Yes	RMPs available in German from PharmNet.Bund
Relief services for patients who have suffered from ADRs	No	No	Yes	In Germany there is no such central service

## **7 COMPANY STRUCTURE FOR PV**

How far does the law dictate the structure of companies regarding pharmacovigilance? Are there specific roles that are required according to local legislation? This section answers these questions.

### **7.1 Company Structure: Europe and the Qualified Person for Pharmacovigilance (QPPV)**

European legislation requires that the MAH has “*permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance in the EU (QPPV)*” (paragraph one of section I.C.1.1, GVP Module 1 “*Pharmacovigilance systems and their quality systems*”, (Ref 30)). GVP Module 1 outlines the role and responsibilities of the QPPV whose name and contact details must be notified to the competent authorities in the EU Member States and the EMA. There can be only QPPV for each pharmacovigilance system; however, one pharmaceutical company can have more than one PV system and allocate a QPPV for each system (Ref 31). A deputy QPPV is also required; both QPPV and deputy must live and work in the EU. GVP Module 1 also gives Member States the option of requiring a PV contact person at national level. Germany makes use of this option and requires a dedicated local PV person. The differences between the German PV person and the QPPV will be explained in the next section.

### **7.2 Company Structure in Germany**

The AMG dictates that every pharmaceutical company which has medicinal products on the market must appoint a local pharmacovigilance responsible person, the “*Stufenplanbeauftragter*” (Graduated Plan Officer), and an “*Informationsbeauftragter*” (Information Officer). These individuals are the key company players in German pharmacovigilance and we will explore the nature of their work and the breadth of their responsibilities in the next two sections.

#### **Stufenplanbeauftragter (Graduated Plan Officer)**

Germany is subject to EU provisions for pharmacovigilance activities, including the requirement in GVP Module 1 for a dedicated qualified person for pharmacovigilance. Germany also has additional national requirements for a local PV person called the

Stufenplanbeauftragter; the official English translation is “Graduated Plan Officer” however BfArM and PEI use the German term even in their English translations. The role and responsibilities of the Stufenplanbeauftragter are given in Section 63 (a) of the AMG and in Section 19 “*Complaints and Product Recall*” of the AMWHV. Every pharmaceutical company which has medicinal products on the market must have a Stufenplanbeauftragter in place.

The following requirements for the Stufenplanbeauftragter must be fulfilled; these requirements are identical to the requirements of the EU QPPV:

- The Stufenplanbeauftragter must reside in Europe,
- The Stufenplanbeauftragter must be qualified and experienced enough to perform his/her duties and
- The Stufenplanbeauftragter must be notified to the relevant competent authorities. Any planned change of the Stufenplanbeauftragter must be notified to the authorities in advance, or as soon as possible after an unforeseen change of Stufenplanbeauftragter.
- A deputy Stufenplanbeauftragter is also required, but this person does not need to be notified to the competent authorities.

There is no *legal* requirement for the Stufenplanbeauftragter to speak German. However, the Stufenplanbeauftragter needs to interact with BfArM/PEI, the federal state authorities, various industry associations of physicians, pharmacists and without speaking excellent German the Stufenplanbeauftragter will not be able to function. The BfArM provides further information in English on their website: [FAQs regarding the Stufenplanbeauftragter](#).

The duties of the graduated plan officer include (taken from Section 63a of the AMG and Section 19 of the AMWHV):

- a. To set up and manage a pharmacovigilance system
- b. To collect reports of medicinal product risks in accordance with procedures laid down in writing, to evaluate such reports as to whether a risk exists, how serious the risk is and what measures are necessary to counter-act the risk.
- c. To inform the qualified person of the risks, so that this person can also fulfil his/her duties, particularly when the issue involves a quality issue
- d. To regularly review the efficacy of the medicinal product.

- e. To take responsibility for the collection of all MP risks reports that are made known in accordance with written procedures and the systematic recording of all product complaints.
- f. To inform the competent authority of every defect which might lead to a product recall or to an abnormal restriction of supply, and to inform the competent authority of other European Member States where the medicinal product is transferred or exported.
- g. To send additional information on the risk-benefit profile of a product, including his/her own evaluations, if required by a competent authority

The role is similar to that of the European QPPV, and a fluent German speaking QPPV can simultaneously hold the position of Stufenplanbeauftragter. However, the Stufenplanbeauftragter also has responsibility for complaints and product recall (as shown in (e) above), which do not fall under the remit of the QPPV. The other main difference is in personal accountability. The wording of the AMG and the AMWHV make it clear that the Stufenplanbeauftragter can be held legally accountable if he/she fails to perform his/her duties; whereas in European Law accountability lies with the legal person of the company. For example, the reporting and taking action about defects is dealt with by European Law under Article 13 of the GMP Directive 2003/94/EC as follows:

- *In the case of medicinal products, the manufacturer shall implement a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network. Any complaint concerning a defect shall be recorded and investigated by the manufacturer. The manufacturer shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply and, in so far as is possible, indicate the countries of destination. (Article 13.1)*

This compares with Section 19.1 and the first sentence of Section 19.2 of the AMWHV which state:

- *The Stufenplanbeauftragter is responsible for the collection of all medicinal product risks reports that are made known in accordance with written procedures and the systematic recording of all product complaints. The careful verification of the reports must thereby be promptly arranged and then evaluated as to whether a medicinal product risk exists, how serious this is and what risk prevention measures are necessary. The necessary measures must be coordinated and the Qualified Person pursuant to Section 14 of the AMG must be informed, so that this*

*person can also take necessary measures if required, particularly when quality issues might be involved. The effectiveness of the procedure must be regularly reviewed. (AMWHV Section 19.1; translation author's own)*

- *The Stufenplanbeauftragter must promptly inform the competent authority of any defect which may lead to a recall or an abnormal restriction of supply and must also disclose to which States\* the medicinal product is transferred or exported. (AMWHV Section 19.2 first sentence, translation author's own) \* States of the European Union*

### **Informationsbeauftragter (Information Officer)**

The roles and responsibilities of the Information Officer are given in Section 74a of the AMG "*Information Officer*". The Information Officer must be qualified/experienced enough to perform his/her duties, and the name of this individual must be notified to the relevant competent authority. The Information Officer is responsible for the content of labelling and advertising.

For labelling, the Information Officer must review and sign off first and subsequent versions of the following, making sure that the content accurately reflects the terms of the marketing authorisation and that regulatory requirements for content and form are complied with for:

- All primary and secondary packaging (for example the blisters that tablets are packed in and the cartons that the blisters go into)
- The package leaflet
- The Summary of Product Characteristics (referred to in the AMG as the "Expert Information")

Advertisements must conform to the specific requirements of Section 8 "*Prohibitions to prevent deception*" of the AMG. This section prohibits the manufacturing or placing on the market of medicinal products/active substances *which bear misleading names, specifications or presentations* (AMG Section 8 (1), point 2).

In addition the Information Officer must check all publications, posters, articles produced by either the company or anyone sponsored by the company.

It should be noted that the Information Officer can also be the Stufenplanbeauftragter, which is a pragmatic solution for small companies. Larger companies may have more

than one Information Officer, for example an Information Officer dedicated for labeling and an Information Officer dedicated for advertising.

### **7.3 Company Structure in Japan**

In Japan all pharmaceutical companies must appoint three key people known collectively as the “triumvirate”; the general marketing compliance manager, the supervisor of drug manufacture and the safety control manager; this structure is a pre-requisite to gaining marketing approval. The appointment of the general marketing compliance manager and supervisor of drug manufacture is specified in Article 17 of the Drugs and Medical Devices Law and the appointment of the safety control manager is specified in Article 4 (2) of the GVP Ordinance Law (Ref 32). The general marketing compliance manager and the safety control manager are the two roles most involved in pharmacovigilance and are described in more detail in the following paragraphs.

#### **General Marketing Compliance Manager/ Safety Control Manager**

The general marketing compliance manager must be a pharmacist (Drugs and Medical Devices Law, Article 17). The Minister of the MHLW can order an MAH to replace the general marketing compliance manager if this person violates the Drugs and Medical Devices Law or any other laws and ordinances related to pharmaceutical affairs (Drugs and Medical Devices Law, Article 73 (Ref 32)).

The safety control manager must fulfil **one** of the following qualification criteria as set out in Article 85 of the Enforcement Regulations:

- 1) A pharmacist
- 2) A graduate of a pharmacology or chemistry course
- 3) Completion of high school courses in pharmacology or chemistry with more than 3 years' experience in quality control or post-marketing safety management
- 4) Confirmation from the minister of the MHLW that the person has knowledge/experience equivalent or greater to 1-3 above.

Further requirements are dependent upon the nature of the drugs that the company is marketing (Ref 33):

- Type 1 marketing authorisation holders are companies that market prescription drugs

- Type 2 marketing authorisation holders are companies that market drugs other than prescription drugs
- Type 3 marketing authorisation holders are companies that market quasi-drugs

**Type 1 MAHs** are subject to the most stringent requirements. The safety control manager must fulfil the following requirements (GVP Ordinance Article 4 (2)):

- must be the head of the Safety Control Unit
- must have more than 3 years of experience of safety assurance activities and other similar duties and functions
- must be able to perform safety assurance activities “*properly and smoothly*”
- must be independent of marketing units.

If safety activities are outsourced, then a Type 1 MAH must appoint a safety control operation manager who can perform activities “*properly and flawlessly*” and who reports to the safety control manager (GVP Ordinance Article 4 (4)).

The general marketing compliance manager must ensure that applicable standard operating procedures (SOPs) are created and available in the office(s) where safety work is performed as follows (taken from GVP Ordinance Article 5):

1. ICSR collection
2. ICSR analysis
3. Implementation of safety measures
4. Reporting procedure of safety control manager to general marketing compliance manager
5. Reporting of safety control operation manager to safety control manager (if applicable)
6. Risk management
7. EPPV (protocol for this must be located in the office of the general marketing compliance manager)
8. Internal audit
9. Education and training of safety unit personnel
10. Retention of records relating to duties and functions of post-marketing safety
11. Cooperation with supervisor of drug manufacture
12. Cooperation with post-marketing surveillance control manager for pharmaceutical risk management

**Type 2 and Type 3 MAHs** are subject to less rigorous requirements. A safety control manager must still be appointed, but the qualifications for this person are not specified.

The establishment of a safety control unit and the appointment of a safety control operation manager for outsourced safety operations are not specified. Written SOPs are also not specified (Articles 13, 14 & 15 of GVP Ordinance).

#### **7.4 Comparative Summary of Company Structure**

Both Germany and Japan require a dedicated person for pharmacovigilance who must possess certain qualifications; in Germany this is the Stufenplanbeauftragter (Graduated Plan Officer) and in Japan this is the safety control manager. In Germany an Informationsbeauftragter (Information Officer) is additionally required, and this person ensures that all items of the labeling (SmPC, package leaflet, packaging) fulfil regulatory requirements and are not misleading. The names of the Stufenplanbeauftragter and the Information Officer must be notified to the relevant higher federal competent authority (BfArM/PEI). The requirements for PV systems and personnel are the same regardless of the type of medicinal product.

In Japan a triumvirate is required of general marketing compliance manager, safety control manager and supervisor of drug manufacture. The Minister of the MHLW can demand that the general marketing compliance manager be replaced if this person violates applicable laws and ordinances. The general marketing compliance manager works together with the safety control manager to guarantee that PV obligations are fulfilled. A safety control operations manager is required if certain safety activities are outsourced. The requirements for pharmacovigilance systems and personnel differ according to the type of drug; MAHs of prescription drugs (Type 1 businesses) are subject to the most stringent requirements.

## **8 PV ACTIVITIES: PRODUCT INFORMATION**

Product information plays arguably the most important role in pharmacovigilance. Product information consists of information for the healthcare professional, the package insert for the patient as well as the packaging (primary and secondary) of the MP. Healthcare professional information gives the precise indication that the product can be used for, has explicit contraindications stating those situations when the product should not be used and contains warnings and precautions for situations when the product should be used with caution. The package insert contributes to patient compliance in the taking of the MP at the correct times and in the correct doses. The packaging shows clearly what is contained in the package and gives immediate information on the most important safety information contained therein. The healthcare professional information, package insert and primary/secondary packaging are referred to in Europe as the “label”.

Product information is a living document that needs to be updated as more information is gathered on the product in the wider clinical setting. New information can result in the tightening or the widening of safety relevant sections (such as indications, contraindications, precautions and warnings). However, there are no ICH guidances on product information. In this section we will compare product information and revisions to product information in Germany and Japan.

### **8.1 Product Information in Germany**

In Germany, as in the rest of the EU, product information is of critical importance and is an official, legal document, mandatory for all medicinal products. Information for the healthcare professional, referred to as the Summary of Product Characteristics (SmPC), together with the package insert and the primary/secondary packaging make up the label. The label including mock-ups of the packaging, is reviewed and approved by the competent authority at the time of marketing authorisation and is updated as further safety information is generated (Ref 34). Changes to safety information contained in product information cannot occur without consultation and approval from the competent authority via a formal variations procedure. Changes to the safety information in the label occur upon request by the MAHs or upon demand by a competent authority/EMA.

Product information is the subject of numerous guidance documents and templates, the most important of which are the Quality Review of Documents (QRD) templates for the SmPC. Two sets of templates are available; the first for MPs authorised through the

centralised procedure and the second for MPs authorised through the national, mutual recognition and decentralised procedure. The template for the centralised procedure is available in English only whereas the template for the national, MRP and DCP procedure is available in German (Ref 35). The EMA webpage also lists 5 Appendices giving standard statements for various sections of the SmPC.

Other information available from EMA includes a list of standard terms for dosage forms, administration routes and containers; a guideline on the SmPC (Ref 36), a guideline on excipients in the label and package leaflet (Ref 37), a guideline on the packaging information (Ref 38), a guideline on the readability of the labelling and package leaflet, guidance regarding Braille requirements for labelling and the package leaflet.

Since 2006 the readability of the label and package leaflet must be assessed by consulting with patients/users as stipulated by article 59 (3) of Directive 2001/83/EC which states that *“The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.”*

In Germany the Information Officer, in accordance with Section 74a, of the AMG of the MAH is responsible for ensuring that product information fulfils requirements. The SmPC is known in German as “Fachinformation” (Expert information) and is mandatory for all marketed MPs; requirements as to content, aligned with European requirements, are given in Section 11a of the AMG. The requirements regarding the content of the package insert are stated in Section 11 *“Packungsbeilage”* of the AMG.

## **8.2 Product Information in Japan**

In Japan product information consists mainly of the package insert, which is a document aimed at healthcare professionals and can be considered as the equivalent of the European SmPC. The package insert was not considered an official document in Japan for a long time and was therefore not subject to review/approval at the time of marketing authorisation application. Changes to the package insert were also left to the discretion of the MAH. The status of the package insert was discussed by the Committee for Investigation of Drug-Induced Hepatitis who recommended in 2009 that the status of the package insert should be clarified and that the package insert should be included as a review item in the MAA process. The Subcommittee on System Reform of the Health Sciences Council recommended in 2011 that MAHs should be obliged to notify the PMDA before producing package inserts at market launch and when revising package inserts.

The package insert now has an official status, but is still not strictly part of the marketing authorisation approval process. Instead responsibility lies with MAHs to draft and update the package insert “based on knowledge obtained from recently published articles related to the drug concerned and other available data” (Article 52, Drugs and Medical Devices Law). However, the MAH must **notify** the PMDA of the package insert for all drugs apart from OTC drugs before marketing starts and at the time of any changes to the “precautions necessary for use and handling” (Article 52-2 of the Drugs and Medical Devices Law, shown in red in Figure 9). The PMDA can request the MAH to make changes to the package insert based on screening results from the PMDA’s ADR database.

<ol style="list-style-type: none"> <li>1 Date of preparation or revision</li> <li>2 Japan Standard Commodity Classification Number</li> <li>3 Therapeutic category</li> <li>4 Regulatory classification</li> <li>5 Name</li> <li><b>6 Warnings</b></li> <li><b>7 Contraindications</b></li> <li>8 Description</li> <li>9 Indications</li> <li>10 Dosage and administration</li> <li><b>11 Precautions</b> <ul style="list-style-type: none"> <li>• <b>Precautions related to the indications</b></li> <li>• <b>Precautions related to the dosage and administration</b></li> <li>• <b>Careful administration</b></li> <li>• <b>Important precautions</b></li> <li>• <b>Drug interactions</b></li> <li>• <b>Adverse reactions</b></li> </ul> </li> </ol>	<ul style="list-style-type: none"> <li>• <b>Geriatric use</b></li> <li>• <b>Use during pregnancy, delivery or lactation</b></li> <li>• <b>Pediatric use</b></li> <li>• <b>Effects on laboratory tests</b></li> <li>• <b>Overdosage</b></li> <li>• <b>Precautions concerning use</b></li> <li>• <b>Other precautions</b></li> <li>12 Pharmacokinetics</li> <li>13 Clinical studies</li> <li>14 Pharmacology</li> <li>15 Physicochemistry</li> <li><b>16 Precautions for handling</b></li> <li>17 Conditions for approval</li> <li>18 Packaging</li> <li>19 References and request for literature should be made to:</li> <li>20 Name and address of manufacturer or importer</li> </ul>
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Figure 9 Outline of package insert showing in red the items related to precautions necessary for use and handling which must be notified to the PMDA (Source: MHLW (Ref 39 ))

Readability tests on the package insert are not required in Japan.

Revisions to the precautions section are published in Japanese and also in English in the PMDA’s “Pharmaceuticals and Medical Devices Safety Information” (excerpt from February 2017 shown in Figure 10 (Ref 40)).

2

Revision of Precautions  
(No. 281)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated January 10, 2017.

---

1

Miscellaneous metabolism agents-Miscellaneous

**Iguratimod**

<b>Brand name</b>	Careram Tablets 25 mg (Eisai Co., Ltd.), Kolbet Tablets 25 mg (Toyama Chemical Co., Ltd.)
<b>Adverse reactions (clinically significant adverse reactions)</b>	Pancytopenia, <u>agranulocytosis</u> , and leukopenia: Pancytopenia, <u>agranulocytosis</u> , and leukopenia may occur. Patients should be carefully monitored through periodic testing, etc. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Figure 10 Revisions of Precautions published in the “Pharmaceuticals and Medical Devices Safety Information” (Source PMDA)

Due to concerns that the information contained in the package insert is too brief, two other supplemental documents aimed at healthcare professionals can be prepared by MAHs (Ref 20). The first is the “Outline of Prescription Pharmaceutical Product Information” which follows the guidelines of the Japan Pharmaceutical Manufacturers Association. The second is the “Pharmaceutical Interview Form” which is based on the 2013 guideline issued by the Japanese Association of Hospital Pharmacists and contains much more detailed information (Ref 41, Ref 42).

### 8.3 Comparative Summary of Product Information

The importance of product information varies considerably between Germany and Japan. In Germany product information encompasses the SmPC, the package insert and primary and secondary packaging. Product information has an official, legal status and must be approved by a competent authority at time of MAA review. Mock-ups and specimens of the inner and outer packaging are also subject to review and approval. Changes in the safety information in the SmPC, package insert & packaging must be reviewed and approved before any change is implemented. Certain information must also be given in Braille. Changes can be at the request of the MAH or as required by a competent authority/EMA. Product information is subject to numerous guidances and templates

available from EMA. In Germany the Information Officer is responsible for the product information. BfArM and PEI do not publish any product information on their websites.

In Japan only the package insert is considered an official document. Mock-ups and specimens of inner and outer packaging are not required during MAA review. Since 2014 MAHs are obliged to notify the PMDA of package insert items relating to the “*Precautions necessary for use and handling*” prior to market launch and revisions to precautions prior to implementation after launch. Changes in the specified items can be proposed by the MAH or may be requested by the PMDA. If proposed by the MAH, then the specified items should be accepted by the PMDA who can also request revisions in the wording. However, neither the PMDA nor the MHLW directly “approve” package inserts. Package insert templates and specific recommendations for wordings are not available. Package inserts submitted by MAHs are published on the PMDA’s website.

## 9 PV ACTIVITIES: RISK MANAGEMENT PLANS (RMPS)

Risk management plans are not covered by the ICH framework. Are RMPs required in Germany and Japan and what parts of the RMP are made public? The next section answers these questions.

### 9.1 RMPs in Germany

The submission of an RMP (a “Risikomanagementplan”) as part of a marketing authorisation application has been mandatory in Germany since 2012, regardless of the authorisation procedure type. A short definition of the RMP is found in Article 4 section 37 of the AMG as “*The risk-management plan is a detailed description of the risk-management system*”, however the outline and content of the RMP is given in Module V of the EU Good Vigilance Practice “*Risk Management Systems*” (Ref 43). The format of the RMP is explained in the document “*Guidance on format of the risk management plan in the EU – in integrated format*” (Ref 44).

The RMP is divided into seven parts:

- Part I Product Overview
- Part II Safety Specifications
  - Module SI Epidemiology of the indication(s) and target population(s)
  - Modules SII Non-clinical part of the safety specification
  - Module SIII Clinical trial exposure
  - Module SIV Populations not studied in clinical trials
  - Module SV Post-authorisation experience
  - Module SVI Additional EU requirements for the safety specification
  - Module SVII Identified and potential risks
  - Module SVIII Summary of the safety concerns
- Part III Pharmacovigilance
- Part IV Plans for post-authorisation safety studies
- Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
- Part VI Summary of the risk management plan
- Part VII Annexes

In accordance with Article 34 section 1a part 3 of the AMG, the risk management plan summary (part VI) is then published on the MP information portal PharmNet.Bund in

either English or German (Ref 45, Ref 46). The summary must be written in easy to read language so that a lay person can also understand it. The list of medicinal products for which RMPs have been published is available from the BfArM website as an excel table (Ref 47).

## **9.2 RMPs in Japan**

Since April 1<sup>st</sup> 2013, MAHs have had to provide an RMP for new drugs applying for marketing/manufacturing approval. RMPs are to be written in Japanese and must be drafted in accordance with the Risk Management Guidance and Templates issued by the PFSA in April 2012; English versions of this guidance and the templates have been provided by the PMDA (Ref 48, Ref 49). In 2013 MHLW published a further Notification announcing their intention to publish sections 1 to 5.3 of RMPs on the PMDA website (Ref 50). The following sections are published:

- Section 1: Summary of Risk Management Plan
- Section 2: Summary of Pharmacovigilance Plan
- Section 3: Summary of Plans for Surveillance and Studies for Efficacy
- Section 4: Summary of Risk Minimization Activities
- Section 5: Lists of Pharmacovigilance Plan, Surveillance and Studies for Efficacy and Risk Minimization Plan

Section 6 is not published – this section gives the name of the following:

- the safety management supervisor,
- the chief administrator of post-marketing surveillance
- the chief administrator of the clinical study plan

As of June 1<sup>st</sup> 2016, 200 RMPs were published on the PMDA website, however results from a survey commissioned by the PMDA showed that only 4.5% of hospitals and 1.7% of pharmacies “fully understand” the information contained in RMPs, and that 36.5% of hospitals and 30% of pharmacies had not heard of RMPs (Ref 51).

## **9.3 Comparative Summary of RMPs**

Risk Management Plans are a required part of the MAA submission in both Germany and Japan. Certain parts of the RMP are made public in both countries. However, the RMP in Germany (and Europe) is a much more comprehensive document than its Japanese counterpart. The EU empty template is 47 pages long excluding annexes whilst the

Japanese empty template is 12 pages with no annexes. A comparison of published RMP sections for the same product (Kovaltry®) showed that in the Japanese version although almost all of the RMP is published, there is no attempt to make this user-friendly for patients and it is doubtful how much even healthcare professionals can understand (Ref 52). The RMP summary in Germany/Europe by contrast was written in lay person language and provides a helpful overview of what the MP is used for, what benefits it has, a summary of safety concerns and how these will be addressed (Ref 53).

## **10 PV ACTIVITIES: INTENSE MONITORING AFTER MARKET LAUNCH**

When a new active substance is launched on the market the safety profile is incomplete. With ICH post-authorisation pharmacovigilance we can expect to learn more about the product's safety profile over the course of the next few years, but what happens in the time directly after product launch? This is a particularly important time as the product will be prescribed and used by professionals who have no experience of the product. This period after launch is not specifically dealt with by ICH, but both Japan and Germany (as part of the EU) are interested in this time and have different mechanisms for pharmacovigilance.

### **10.1 Intense Monitoring after Market Launch in Germany (and EU)**

Since autumn of 2013, certain MPs in the European Union have been subject to intense monitoring for a period of five years or until EMA's Pharmacovigilance Risk Assessment Committee (PRAC) decides that it no longer needs to be intensely monitored. The MPs that are subject to intense monitoring are known as "Medicines under additional monitoring" and are identified with an inverted black triangle on their package leaflets and SmPCs with a short sentence next to the triangle "*This medicinal product is subject to additional monitoring*" (Ref 54).

The following MPs are subject to additional monitoring in the EU:

- MPs containing a new active substance authorised in the EU after 1<sup>st</sup> January 2011
- Biological medicines (vaccines or blood-derived products)
- MPs authorised under the conditional approval/exceptional circumstances routes
- MPs which are approved subject to post-authorisation safety studies (PASS)
- Any MP that PRAC recommends be placed under additional monitoring

A European list is available which details all medicines subject to additional monitoring; the list is reviewed monthly by PRAC and as of February 2017 contained 319 active substances (Ref 55) (Figure 11). The requirement for EMA to provide this list is given in Article 23 of Regulation EC 726/2004 and Article 11 of Directive 2001/83/EC. The GVP

guideline covering this topic is Module X “Additional Monitoring” and the use of the inverted black triangle is stipulated in the Implementing Regulation EU 198/2013 (Ref 56).



29 March 2017  
 EMA/245297/2013 Rev.43  
 Inspections & Human Medicines  
 Pharmacovigilance

List of medicinal products under additional monitoring

**Related Information:**

[Additional monitoring explained:](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000365.jsp)  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/special\\_topics/document\\_listing/document\\_listing\\_000365.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000365.jsp)

[Good Pharmacovigilance Practice Module on additional monitoring:](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp)  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000345.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp)

**To note: All products added to the list in March 2017 are shown in red font. All products removed from the list are**

Product name	Active Substance (s)	Reason (s) on list
Abasaglar (previously Abasria)	Insulin glargine	New biological
Acarizax	Standardised allergen extract from house dust mites	New Biological
Accofil	Filgrastim	New biological
Adcetris	Brentuximab vedotin	New active substance, conditional authorisation
Adempas	Riociguat	New active substance

Figure 11 Excerpt from the EU list of medicinal products under additional monitoring (Source EMA Website, March 2017)

In Germany, MPs subject to additional monitoring are referred to as “*Arzneimittel unter zusätzlicher Überwachung*”, the black triangle is known as “*das schwarze Dreieck*” and is shown with the sentence “*Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung*” (“This medicinal product is subject to additional monitoring”) (Figure 12) (Ref 57).



Figure 12 Black triangle and text as is appears on package inserts and SmPCs on the German market.

The black triangle alerts healthcare professionals and patients to the fact that the product is subject to additional monitoring and urges them to report any suspected adverse reactions.

In Germany the Information Officer is responsible for ensuring that MPs subject to additional monitoring are correctly identified in the package leaflet and SmPC.

## 10.2 Intense Monitoring after Market Launch in Japan

Intense monitoring of certain drugs after launch was introduced in Japan in 2001 as the “Early Post-Marketing Phase Vigilance” (EPPV) system. EPPV applies to drugs defined in Article 14-4 (1) of the Drugs and Medical Devices Law, i.e. drugs for which any of the following items are **clearly different from drugs already on the market** (Ref 21).

- active substance
- quantity of active substance
- dosage
- administration
- indications

Drugs can be exempted if there is a “*rational reason not to conduct EPPV*” (Answer 1 from Q&A on EPPV for Prescription Drugs” (Ref 58).

The MAH of such newly approved drugs is required to perform EPPV actions as stipulated by Article 10 of the Japanese GVP Ordinance. The EPPV plan must be submitted by the applicant as part of the marketing authorisation application and adherence to the approved plan is one of the conditions of approval. The Safety Control Manager is responsible for the implementation of the EPPV plan.

The EPPV is a mixture between detailed surveillance and concentrated information for medical institutions (hospitals and clinics but not dispensing pharmacies) to which the product will be supplied. EPPV actions must be carried out by the MAH (or an outsource company working on behalf of the MAH) over a 6-month time-period from the introduction of the medicinal product onto the Japanese market. MAHs must contact all medical institutions to which their product will be supplied for the following reasons:

- to inform medical institutions that the new drug is subject to EPPV
- to inform medical institutions of the start and end of the EPPV period
- to explain to medical institutions how to use the new drug appropriately
- to ask for cooperation in reporting ADRs

- to provide updates as necessary throughout the EPPV period.

Contact between MAH and medical institutions can be by mail, fax or e-mail but must be followed up with personal contact by the medical representatives (MRs) of the MAH. An EPPV report must be submitted to the PMDA two months after the EPPV has ended (Figure 13).

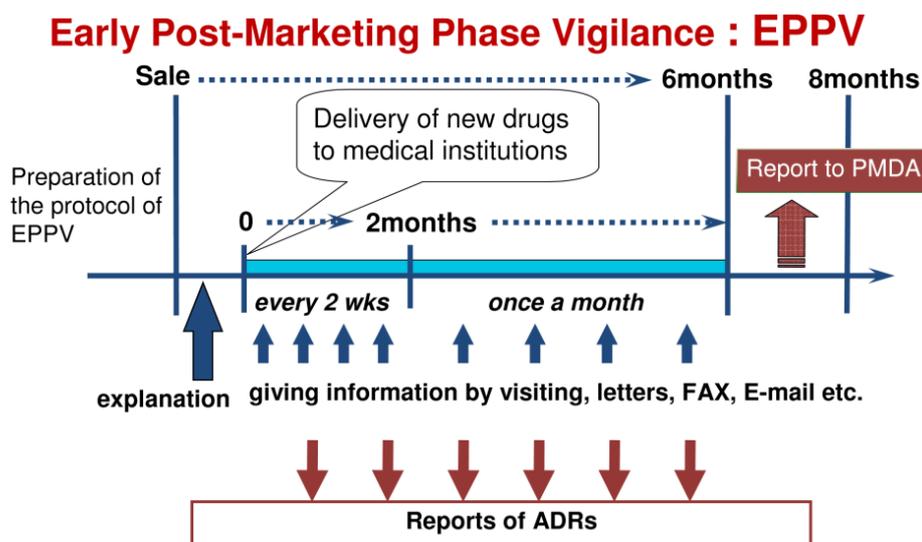


Figure 13 Overview of EPPV Process (Source PMDA (Ref 59))

A list of new drugs that are subject to EPPV is updated monthly by the PMDA and published in Japanese and also in English in the “Pharmaceuticals and Medical Devices Safety Information”. The list contains the non-proprietary and brand names of the drugs, the MAHs and the EPPV start date. The February 2017 PMDSI update lists the current 36 drugs subject to EPPV (Ref 40) (Figure 14).

3

## List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its marketing authorization holder (MAH) is responsible for collecting adverse drug reaction (ADR) from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of December 31, 2016)

⊙: Products for which EPPV was initiated after December 1, 2016

Nonproprietary name		Name of the MAH	Date of EPPV initiate
Brand name			
⊙	Carbapenem Carbapenem Dispersible Tablets 200 mg	Pola Pharma Inc.	December 22, 2016
⊙	Canakinumab (Genetical Recombination) Ilaris for Subcutaneous Injection 150 mg <sup>*1</sup>	Novartis Pharma K.K.	December 19, 2016
⊙	Eplerenone Selara Tablets 25, 50 mg <sup>*2</sup>	Pfizer Japan Inc.	December 19, 2016

Figure 14 Excerpt from PMDA List of Drugs subject to EPPV (Source PMDSI No. 340, Feb 2017)

Guidance on the EPPV is provided in the PFSB’s Notification “Implementation Methods, etc. of Early Post-Marketing Phase Vigilance for Prescription Drugs”; an English version of this has been made available by the PFSB and includes templates for the EPPV plan and the EPPV report (Ref 60). Further information is available in the PFSB’s Notification “Q&A on Early Post-marketing Phase Vigilance for Prescription Drugs”.

### 10.3 Comparative Summary of Intense Monitoring after Market Launch

Both Germany (as part of the EU) and Japan have mechanisms for intense monitoring; however the products subject to monitoring, the length/type of monitoring and person responsible for monitoring differ between the two countries (Table 5).

Table 5 Comparison of German & Japanese Intense Monitoring Schemes

	<b>Germany</b>	<b>Japan</b>
Name of monitoring scheme	Medicines under additional monitoring	Early Post-marketing Phase Vigilance (EPPV)
Products subject to monitoring	<ul style="list-style-type: none"> <li>• all new active substances</li> <li>• all biologics</li> <li>• MPs authorised through conditional approval/exceptional circumstances</li> <li>• MPs subject to PASS</li> <li>• any MP identified by PRAC</li> </ul>	<ul style="list-style-type: none"> <li>• new active substances</li> <li>• new quantities of active substances</li> <li>• new dosages/administration routes</li> <li>• new indications</li> </ul>
Length of monitoring	5 years or until PRAC removes MP from list	6 months
Type of monitoring	Passive: Black symbol on package insert and SmPC, request to HCPs and patients to report suspected ADRs	Active: Intense communication between medical reps and medical institutions where product is supplied
Person responsible for implementation	Information Officer	Safety Control Manager

## 11 PV ACTIVITIES: POST-AUTHORISATION SAFETY REPORTING

Expedited post-authorisation reporting is partially harmonised within ICH regions with the E2D guideline which gives definitions of seriousness and expectedness and sets the reporting time frame of 15 calendar days for serious, unexpected ADRs. However, ICH allows for other time frames for other types of reports and also allows for interpretation of “medically important events” which should be classed as serious (Ref 5). In this section we will look at whether other time frames are given for other serious ADRs and how medically important events are defined.

### 11.1 Post-Authorisation Safety Reporting in Germany

#### Expedited Reporting

Expedited post-authorisation safety reporting is dealt with in accordance with article 63c of the AMG. Only suspected adverse reactions must be reported, i.e. those reactions where causality with the medicinal product cannot be ruled out. The major sources of safety reports are:

- Healthcare Professionals
- Patients
- Literature reports

The MAH must electronically inform the relevant higher federal CA for the product (either BfArM or PEI) of **suspected, serious** adverse reactions which occur in Germany or in a third country within 15 days of gaining knowledge of the reaction; regardless of expectedness. Suspected serious cases which occur in a third country must in parallel be reported to EMA until the European EudraVigilance database is fully functional in November 2017, after which all suspected serious adverse reactions will be reported via this database (Ref 61). A third country is defined as a non-European Economic Area (EEA) country (the EEA countries being the 28 EU Member States plus Iceland, Lichtenstein and Norway). Suspected, serious adverse reactions from other EEA countries do not have to be reported to BfArM/PEI.

The EMA gives guidance on important medical events (IMEs) which can be classed as serious with an important medical events terms list (based on MedDRA version 19.1), a comprehensive list with over 8,000 preferred term entries (Ref 62) (Figure 15).



27 March 2017  
EMA/207864/2017  
Inspections, Human Medicines Pharmacovigilance & Committees Division

**Important medical event terms list (MedDRA version 20.0)**

MedDRA Code	SOC Name	PT Name	Comment
10078862	Blood and lymphatic system disorders	Hyperleukocytosis	This term fits the inclusion criteria for important n immediately life-threatening or result in death or the patient or may require intervention to prevent disability/incapacity. Hyperleukocytosis refers to : that has been variably defined as a total leukemi x 10 <sup>9</sup> /L (50,000/microL) or 100 x 10 <sup>9</sup> /L (100,000
10078778	Blood and lymphatic system disorders	IDH differentiation syndrome	IDH differentiation syndrome is a potentially fatal treatment, and the underlying pathophysiology is differentiation syndrome, a potentially fatal comp treatment, fits the inclusion criteria for important immediately life-threatening or result in death or the patient or may require intervention to prevent disability/incapacity.

Figure 15 Excerpt from EMA’s Important medical event terms list (EMA Website, March 2017)

**Suspected non-serious** adverse reactions should be electronically reported by the MAH to the BfArM/PEI within 90 days of receipt if required.

Adverse reaction reports do not have to be kept in Germany, but must be kept available at a central location, which belongs to the MAH, within the European Union.

### Periodic Safety Update Reports (PSURs)

The submission of PSURs is mandatory under Article 63d of the AMG. However, content and location of submission is determined by European regulations. The content of the PSURs is described comprehensively in the Module VII GVP 68-page Guideline “*Periodic Safety Report*” (Ref 63) which is based on the ICH E2C(R2) Guideline “*Periodic Benefit-Risk Evaluation Report*” (Ref 64) and will not be further elucidated here.

A new requirement from 13<sup>th</sup> June 2016 is that the MAH no longer submits the PSURs to BfArM/PEI; instead they are submitted to the central European PSUR repository for assessment by EMA (Ref 65). This requirement applies to all PSURs, regardless of the authorisation procedure (national, centralised etc.) used.

The frequency of PSUR submission is set at a European level by the list of European Union Reference Dates (EURD list) for active substances and combinations. The EURD harmonises data lock points and submission dates by active substance, allowing the EMA

to perform a single assessment of all PSURs related to the active substance concerned. The EURD list is an Excel list available from the EMA PSUR homepage (Ref 65).

Only if the active substance/combination is not in the EURD list should the MAH submit the PSUR to the national authority at either the standard frequency or the frequency specified at the time of approval of the marketing authorisation. The standard frequency is every 6 months from authorisation until the MP is marketed; once the MP is marketed it is every 6 months for the first 2 years, then once a year for the following two years and after that every 3 years (Figure 16).

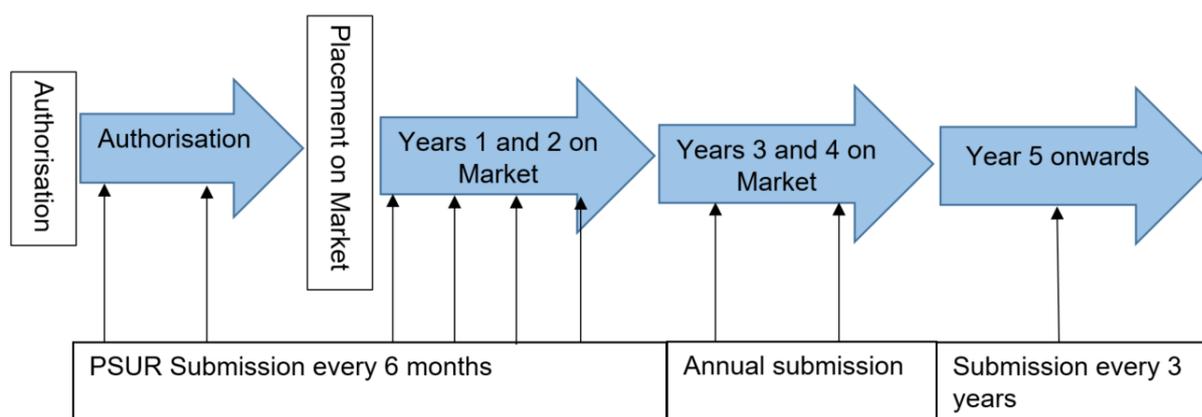


Figure 16 Standard submission frequency of PSURs not on the EURD list

## 11.2 Post-Authorisation Safety Reporting in Japan

### Expedited Reporting

The time-frames for expedited reporting are set out in Article 228-20 “Adverse Reaction Reports” of the Enforcement Regulations, and are explained in more detail in the PFSB Notification 1002/20 dated 2<sup>nd</sup> October 2014 (Ref 66). The timelines are quite complex, a simplified version is offered here as follows:

- All **suspected, serious** adverse reactions occurring in Japan are subject to expedited reporting of either 15 or 30 days depending on the expectedness of the occurrence; all **unexpected serious adverse reactions** must be reported within 15 days.
- **Deaths** classed as “**expected**” must be reported within 15 days, other **serious, expected adverse reactions** must be reported within 30 days.

- For adverse reactions occurring outside of Japan, only **unexpected serious adverse reactions** are subject to expedited reporting within 15 days.
- Reports of **unexpected infections** occurring both inside and outside Japan suspected to be caused by the drug must be reported within 15 days.
- Reports of **unexpected onset patterns of serious adverse reactions** occurring both inside and outside Japan must be reported within 15 days.
- Reports of **unexpected changes in onset patterns** both inside and outside Japan which “*might cause or spread hazards to public health and hygiene*” must also be reported within 15 days (Enforcement Regulations Article 228-20,1b ii).

### **Periodic Benefit Risk Evaluation Reports (PBRERs)**

The submission of PBRERs is mandatory under Article 63 “*Periodic Safety Reports*” of the Enforcement regulations. The report is based on the ICH E2C(R2) PBRER and detailed notifications concerning this report were published on the 17<sup>th</sup> of September 2013 (PFSB/SD 0917/2), on the 16<sup>th</sup> of February 2015 (PFSB/SD 0216/2), on the 28<sup>th</sup> of September 2015 (Q&As) and on the 31<sup>st</sup> of March 2016 as notification PFSB/SD 0331/9 (all data available in Japanese only from the PMDA website, Ref 67).

The PBRER must be submitted in Japanese to the MHLW and the contents of the report must show data for the drug in Japan and data for the drug overseas (if applicable).

The submission frequency is set at every 6 months from approval for the first two years and then annually until the re-examination procedure.

## **11.3 Comparative Summary of Post-Authorisation Safety Reporting**

Both countries have expedited reporting for serious ADRs. In Germany all serious ADRs occurring in Germany, regardless of expectedness, must be reported to the competent authority within 15 days. EMA publishes a list of IMEs which MAHs must consider when deciding if an ADR is serious or not. BfArM/PEI can request that all non-serious ADRs are reported within 90 days. Otherwise non-serious ADRs are submitted with the PSUR.

In Japan there are two expedited timelines, depending on the expectedness of the ADR. All serious unexpected ADRs and deaths classed as expected must be reported within 15 days. Serious, expected ADRs (apart from death) must be reported within 30 days. A list of IMEs is not available, but unexpected infections, unexpected onset patterns or changes in onset patterns must be reported within 15 days.

Non-expedited reporting is mandatory and covered by PSURs in Germany and PBRERs in Japan. In Germany PSURs are uploaded onto a European platform at the timing set by the European Union Reference Date List.

## **12 PV ACTIVITIES: DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)**

If the MAH becomes aware of an urgent health risk, then it must alert competent authorities and healthcare professionals about these risks as soon as possible. Urgent health risks for marketed products can arise for the following reasons:

- New contraindications that must be communicated immediately
- New serious adverse drug reactions that the MAH has become aware of
- Quality issues that require batch recall
- A marketing authorisation that has been suspended, withdrawn or revoked due to safety concerns
- Supply shortages that may affect patient care
- Falsified products that have entered the supply chain

A CA may also instruct MAHs to issue DHPCs if it becomes aware of a safety issue, for example through the publication of a new study.

ICH has no guidelines on this topic. The EU gives guidance on new and emerging safety information in GVP Module XV “Safety Communication” and in the Annex II Template “Direct Healthcare Professional Communication” (Ref 68, Ref 69).

### **12.1 DHPC in Germany**

In Germany, the MAH can contact healthcare professionals directly using either an “Information Letter” (“Informationsbrief”) or a “Red Hand letter” (“Rote-Hand-Brief”). Information Letters are sent when the aim is to inform healthcare professionals, whereas Red Hand letters are sent when the healthcare professional is required to take action. Both types of letter must be submitted for review to the relevant authority (either BfArM or PEI) before being issued.

#### **Language Used**

Information Letters and Red Hand letters must be submitted to the authority in German and it is left to the MAH’s discretion as to whether to submit also in English. Of the 29 letters published on the BfArM website from 1<sup>st</sup> January to 20<sup>th</sup> November 2016, 11 were Information Letters (8 of which were also published in English) and 18 were Red Hand Letters (15 of which were also published in English). In the same period, 1 Information

Letter and 2 Red Hand Letters were issued on the PEI site; none of which were available in English. MAHs should therefore be aware that if they wish to see the full list of letters they must look in the German sections.

### Relevant webpages

All letters concerning BfArM regulated products are published in German on the BfArM site in the section “[Rote-Hand-Briefe und Informationsbriefe](#)”; English versions are found under “[Rote-Hand-Briefe and Information Letters](#)”. Letters concerning PEI regulated products are published on the PEI site in German in the [Rote-Hand-Briefe](#) section and only a few are published in English in the [Safety Alerts](#) section.

### Information Letters: Format, Content and Addressees

Content: Information Letters contain the information set out in the Annex II template from the EMA as follows:

- Date
- Heading which includes the name of the Medicinal Product
- Summary (in German “Zusammenfassung“)
- Call for Reporting (in German “Aufforderung zur Meldung/Aufruf zur Meldung von Nebenwirkungen“)
- Company contact point (in German “Ansprechpartner des Unternehmens/Kontaktdaten der beteiligten Firmen“)

### Red Hand Letters: Format, Content and Addressees

The Red Hand letters get their name from the distinctive picture of a red hand which is placed at the top right or top left corner of the letter and in the middle of the hand it states “Important notification about a medicinal product” (in German “wichtige Mitteilung über ein Arzneimittel”) as shown in Figure 17:



Figure 17 The red hand logo which must appear on Red Hand letters.

This distinctive logo was developed by the German Pharmaceutical Industry Association (the BPI: Bundesverband der Pharmazeutische Industrie e.V.) and started as a voluntary commitment by member companies when sending important and urgent safety information. Over time it became so established that it became a requirement to use this logo, regardless of whether the MAH is a member of this organisation or not (Ref 70).

### **Format**

BfArM and PEI do not provide any templates for the Red Hand letters, but the accepted format is that the logo must appear in the top right or left hand corner of the letter, the company logo is then placed in the other top corner of the letter. This red hand must also appear on the envelopes in which the letter is sent.

### **Content**

The content of the Red Hand letters is flexible so that it can be used for a variety of reasons. The layout of the content is the same as in the annex II template described above. BfArM/PEI must agree with the content, the addressees and the timeline for action before the Rote Hand letter can be issued.

### **Addressees**

Once agreed by the CA, the Rote Hand letter can be issued. It is published on the BfArM or PEI website in electronic form, and must also be sent to the following:

- Concerned doctors and pharmacists in hospitals
- Concerned general practitioners and local pharmacies
- The Drug Commission of the German Medical Association (Arzneimittelkommission der deutschen Ärzteschaft )
- The Drug Commission of German Pharmacists (Arzneimittelkommission der Deutschen Apotheker)
- The federal state authorities
- All those involved in the graduated plan

The MAH also needs to consider the indication, distribution network and relevant expert groups in order to decide who else needs to receive this letter. The MAH should also publish this Rote Hand letter on its own website.

## 12.2 DHPC in Japan

Japan operates a similar system and an MAH can communicate important new safety information directly to healthcare professionals using either a “Yellow Letter” for emergency safety information or “Blue Letter” for rapid safety information. This is anchored in the Drugs and Medical Devices Law in Article 68-9 (1) “Prevention of Hazards”, which states that MAHs must take any necessary measures to prevent hazards including “*disposal, recall, suspension of sales and **supply of data** to prevent such hazards*”.

### Language Used

Both yellow and blue letters must be submitted in Japanese to the PMDA and can also be submitted in English. The PMDA and the MHLW both publish these letters on their websites; the PMDA site has some letters also in English whereas the MHLW site publishes only the Japanese letters. The PMDA also sends alerts of yellow and blue letters to Healthcare Professionals who subscribe to the PMDA medi-navi system.

### Relevant webpages

Yellow and blue letters are published in Japanese on the PMDA site in the section [緊急安全性情報（イエローレター）・安全性速報（ブルーレター）](#) and English versions are found in the section [“The Yellow Letter / Blue Letter”](#) . Japanese versions only are published on the MHLW site in the section [“緊急安全性情報／安全性速報”](#).

### Addressees

As well as being published on the PMDA and MHLW websites, MAHs must publish yellow and blue letters on their company websites and information must be “*directly provided to the medical institutions, pharmacies and other facilities where the product is delivered via information brochures distributed by medical representatives, direct mail, fax and/or email within 1 month.*” (from the “*Guidelines for Provision of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications*” (Ref 71)).

After distribution of the yellow/blue letters and information brochures, the MAH and PMDA may issue press releases if warranted by the urgency of the situation. If the general public are affected by the situation (for example when a product is recalled) then the MAH must also publish an announcement about this in the newspapers.

## Content

The content of yellow and blue letters is flexible so that it can be used for a variety of reasons. However, the following information is always present:

- Date at the top of the page
- Heading which includes the name of the medicinal product involved
- A summary of the situation in the first paragraph
- Information on what HCPs should do
- Company contact point

### Format of Yellow Letters for Emergency Safety Information

The PMDA does not offer any template for yellow letters but the accepted format is that they are issued on yellow paper with the wording “Emergency Safety Information (緊急安全性情報 “Kinkyuu Anzensei Jouhou”) at the top of the page and the word “Important” (重要; “Juuyou”) written diagonally on the top left corner (Figure 18).



Figure 18 Latest example of a yellow letter issued in March 2007.

### Format of Blue Letters for Rapid Safety Information

Blue Letters are for rapid safety information and are issued on blue paper with the wording “Safety Information” (安全性情報 “Anzensei Jouhou”) at the top of the page and the word “Important” (重要; “Juuyou”) written diagonally on the top right corner (Figure 19).



Figure 19 Latest example of a blue letter issued in February 2015.

### 12.3 Comparative Summary of DHPC

Both Germany and Japan have systems for sending urgent safety information via DHPC. In Germany the “Red Hand Letter” is used when HCPs are required to take action; in Japan the “Yellow Letter” or “Blue Letter” is used.

However, the numbers from the past 4 years reveal that the “Red Hand Letter” system in Germany is used much more widely than the “Yellow Letter/Blue Letter” system in Japan (Table 6) (figures taken from those published on PMDA Japanese website and BfArM/PEI German websites)

Table 6 Numbers of DHPCs in Germany and Japan from 2013-2016

Year	Germany		Japan	
	No. of Red Hand Letters*	No. of Information Letters*	No. of Yellow Letters	# of Blue Letters
2016	21	14	0	0
2015	16	9	0	1
2014	28	21	0	3
2013	52	23	0	1

\*=Combined number from BfArM and PEI

## **13 SUMMARY**

The aim of this thesis was to help pharmaceutical professional understand the pharmacovigilance environment in Germany and Japan by comparing the systems in each country. The main points from each section are summarised in the paragraphs below.

### **International Framework**

It has been shown how both Germany and Japan fit into the international ICH PV framework and how Germany fits into the EU PV framework. The ICH PV framework suffers from lack of development which has lead to regions developing their own PV requirements. The EU has developed a comprehensive set of GVP modules which are mandatory in Germany.

### **Pharmacovigilance Overview**

The main events which have shaped attitudes towards pharmacovigilance have been introduced and assessed. Germany, with its legacy of the thalidomide tragedy, has an approach of obligations imposed on MAHs and competent authorities empowered to demand changes and conduct inspections. Japan, with its legacy of hepatitis and AIDs tragedies, shares responsibilities between citizens, health-care professionals, MAHs, the ministry and the PMDA.

### **Legal Framework**

The legal framework of laws, ordinances and notifications surrounding pharmacovigilance in Germany and Japan have been introduced and links to English versions have been given wherever possible. Germany has a relatively simple linking of law, ordinance and notifications. The EU directives and regulations are written straight into the main German law. The AMG and AMWHV are stand-alone documents. By contrast the legal framework in Japan is more complex with one law, one cabinet enforcement ordinance, one ministerial enforcement regulation and numerous ministerial ordinances and notifications. The law is not a stand-alone document but must be read in conjunction with the enforcement ordinance and regulations. ICH requirements are not directly written into the law but are published through ministerial notifications.

### **Ministries and Authorities**

The ministries and authorities responsible for pharmacovigilance have been introduced and an overview of their main activities has been given. Germany has two competent

authorities, BfArM and PEI, which act as one-stop shops for pharmacovigilance as they are empowered to grant marketing authorisations/renewals, to place conditions on marketing authorisations and to conduct pharmacovigilance inspections. BfArM and PEI differ only in the products for which they are responsible; BfArM is responsible for MPs and medical devices, PEI is responsible for biologics.

Japan has one agency, the PMDA, which reviews marketing authorisations but does not grant approval; this power is reserved for the MHLW. The PMDA has certain additional responsibilities, such as the administering of funds to patients who have suffered ADRs and the publishing of RMPs/package leaflets, which are not mirrored in BfArM/PEI.

### **Company Structure**

Legal requirements for company structures have been explained. In Germany two posts are key for pharmacovigilance; that of the Stufenplanbeauftragter and the Information Officer. The Stufenplanbeauftragter is similar to a European qualified person for pharmacovigilance, except that the Stufenplanbeauftragter has personal liability and is also responsible for product quality complaints. The Information Officer is responsible for the label. The requirements for the Stufenplanbeauftragter and Information Officer are independent of what type of medicinal products the company markets and the names of these personnel must be notified to the authorities.

In Japan a triumvirate is required as a condition of marketing authorisation approval, consisting of the general marketing compliance manager, the safety control manager and the supervisor of drug manufacture. The general marketing compliance manager must be a pharmacist and must be replaced if the minister of the MHLW demands this due to violations of applicable laws or ordinances. Requirements as to written procedures and personnel depend upon the product being marketed; the most stringent requirements are for prescription drugs.

### **Routine Pharmacovigilance Activities**

Routine pharmacovigilance activities are defined by ICH and are similar between Germany and Japan. Post-authorisation pharmacovigilance starts with the submission of the risk management plan and product information as part of the marketing authorisations application. The German risk management plan is more comprehensive than the Japanese plan; parts of RMPs in both countries must be published but in Europe there is an additional requirement for the published part to be written in language that a lay-person can understand.

Product information varies greatly between the countries, in Germany the entire label (SmPC, Package leaflet and primary and secondary packaging) is part of the MAA review and mock-ups and specimens are required. The German label is an official document with a legal status and safety information can only be changed after submission and approval by a competent authority. By contrast in Japan only the package insert has official status and this is “accepted” by PMDA but not “approved” and MAHs are required merely to notify the PMDA before changing any sections of the precautions and use for handling.

Both countries have mechanisms in place for intense monitoring after market-launch however there are great differences in the length of time that the medicinal product is monitored (5 years in Germany, 6 months in Japan) and the way that the product is monitored (heightened awareness for HCPs and patients to report in Europe, vs. active, intense monitoring of medical institutions by medical representatives in Japan).

Expedited reporting has slightly different timelines between Germany and Japan; in Germany, there is a 15 day timeline for all serious ADRs occurring within Germany, in Japan the timeline is 15 days or 30 days for serious ADRs depending on the expectedness. In Germany, the European list of important medical events must be consulted as part of the seriousness evaluation, in Japan there is no such list of important medical events, but all unexpected infections must be reported within 15 days.

Periodic safety reporting is performed in both countries and is submitted in Germany as the Periodic Safety Update Report at a timeline set by the European Union Reference Date list; in Japan this is submitted as a Periodic Benefit-Risk Evaluation Report at a timeline set at the time of approval. Both countries have mechanisms in place for direct healthcare professional communications, but whilst this mechanism is used frequently in Germany with the “Red Hand Letter” system, the Japanese equivalent of yellow and blue letters remains a theoretical mechanism which is not used in practice.

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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.

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Ort, Datum

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Unterschrift