Simplification Instead of Complication: A Critical Assessment of Pharmacovigilance Legislation from an Industry Perspective

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Table of Content

List of Figures

List of Tables

General remarks

A short explanation must be given in terms of reference style, consisting of the source number and the respective chapter or section in brackets and the abbreviations “p.” or “pp.” are used referring to “page” or “pages”.

It must also be noted that references are not always made to a specific page but also chapters, sections or articles, which at times may be a source of confusion for the reader of this thesis. Unfortunately, it was not possible to edit or rename the “p.” and “pp.” due to a technical bug in the reference software which the developer has yet to fix.

List of abbreviations

Abbreviation	Full Text
AE	Adverse Event
AKdÄ	Drug Commission of the German Medical Association (German: Arzneimittelkommission der deutschen Ärzteschaft)
AMG	Arzneimittelgesetz (English: Medicinal Products Act)
AMK	Federal Union of German Associations of Pharmacists (German: Arzneimittelkommission der deutschen Apotheker)
aRMM	additional Risk Minimisation Measure
BfArM	Federal Institute for Drugs and Medical Devices (German: Bundesinstitut für Arzneimittel und Medizinprodukte)
BPI	German Pharmaceutical Industry Association (German: Bundesverband für Pharmazeutische Industrie)
CAPA	Corrective Action Preventative Action
cd	calendar day
DHPC	Direct Healthcare Professional Communication
DIR	Directive
DLP	Data Lock Point
DUS	Drug Utilisation Study
EC	European Commission
EM	Educational Material
EMA	European Medicines Agency
EPITT	European Pharmacovigilance Issues Tracking Tool
eRMRs	electronic Reaction Monitoring Reports
ESI	Emerging Safety Issue
EU	European Union
EURD	European Union Reference Dates
EV	EudraVigilance
EVDAS	EudraVigilance Data Analysis System
EVWEB	EV Web Application
GVP	Good Pharmacovigilance Practice
HaRP	Harmonisation of RMP Project
HCP	Health Care Professional

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IN	Immediate Notification
IR	Implementing Regulation
IT	Information Technology
KPI	Key Performance Indicators
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MB	Megabyte
MLM	Medical Literature Monitoring
mo	months
NCA	National Competent Authority
OTC	Over The Counter
PAES	Post-Authorisation Efficacy Study
PASS	Post- Authorisation Safety Study
PEI	Federal Institute for Vaccines and Biomedical Drugs (German: Paul Ehrlich Institute)
PI	Product Information
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance Safety Master File
PSUR	Periodic Safety Update Report
PSUSA	PSUR Single Assessment
PV	Pharmacovigilance
QPPV	Qualified Person Pharmacovigilance
QR code	Quick Response code
RA	Regulatory Affairs
REG	Regulation
RHB	Red Hand Letter (German: Rote Hand Brief)
rRMM	routine Risk Minimisation Measure
RMP	Risk Management Plan
RMS	Reference Member State
Rx	prescription only medicinal product

SMP	Signal Management Process
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
URL	Uniform Resource Locator
US	United States
WHO	World Health Organisation

1 Introduction

1.1 Intention of the thesis

The 2012 amendments to EU Pharmacovigilance (PV) legislation were one of the most significant changes to European medicinal product legislation since the introduction of the PV requirements in 1995. As a result, the pharmaceutical industry has faced major challenges in dealing with the growing body of legislation, due to the necessary adaptations to systems and processes and significant investment of resources to provide the required documentation or implement recommendations from EMA (European Medicines Agency) committees.
From an industry perspective, it has become necessary to illustrate the consequences of this increasing difficulty to comply with legislative requirements (e.g. a massive increase in personnel costs) as well as highlight those areas where further rule adaptations are not necessary and should be avoided.
Furthermore, consolidation, clarification or harmonisation of existing legislation could potentially lead to more efficient and staff-friendly processes for the pharmaceutical industry, while maintaining the highest quality standards and ensuring the safety of the medicinal product for the patient and user. This master thesis will discuss these industry perspectives, thus its title is **"Simplification Instead of Complication"**.

Recently, the BPI (German Pharmaceutical Industry Association; German: Bundesverband für Pharmazeutische Industrie) started an in-depth look into "PV hot topics" together with industry representatives in order to identify and analyse existing issues and challenges as well as their implications for industry. The conclusions and recommendations were published in April 2020 as a series of papers titled "Pharmacovigilance and Maintenance of Medicinal Products" [1].

This master thesis will select and discuss several of the PV hot topics which are causing difficulties for industry. It must however be noted that PV issues can hardly be approached in isolation as they are heavily interrelated and overlap significantly (which is partly why they represent such a challenge for industry) cannot be discussed in isolation from each other. Chapter 2 of this thesis visualizes these processes and defines their "Inputs" and "Outputs" in order to make the interfaces between the processes visible. The result was a simplified PV network, represented in Figure 1.

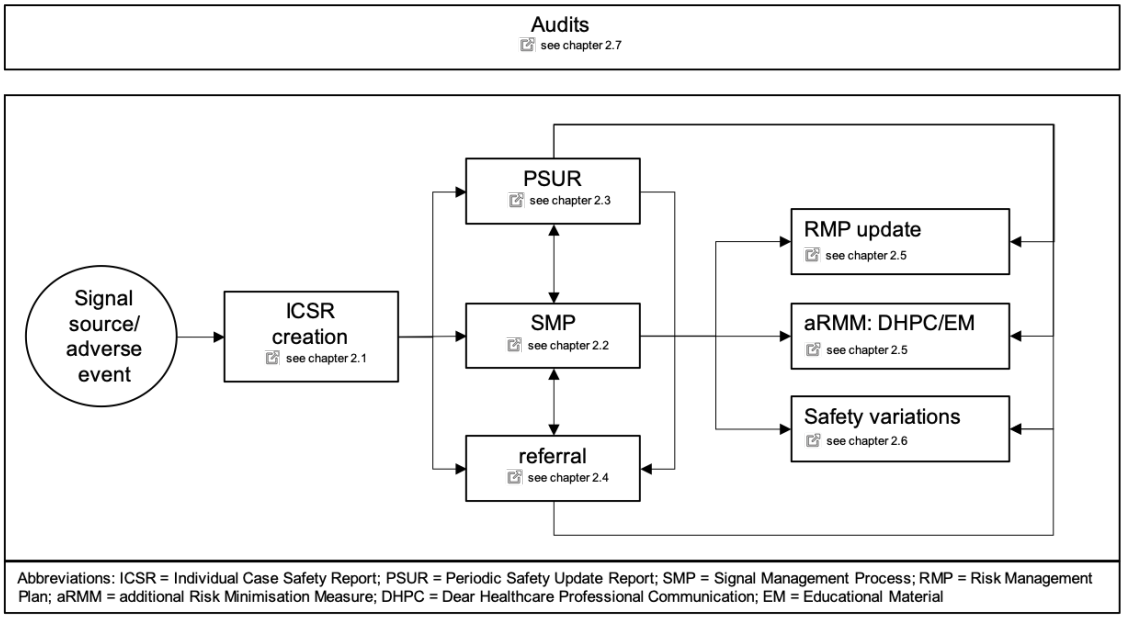

Figure 1: Simplified overview of the PV network – the big picture

The objective of this thesis is not to exhaustively list and describe all legal PV requirements and the whole PV system in Europe, but instead will focus on the most important topics addressed by the paper series.

As visible in Figure 1, the signal source/adverse event (AE) is generally the trigger for all further PV processes, which is not surprising considering that most PV topics are related to keeping the safety profile of a medicinal product up to date as well as to take appropriate measures in case of an adverse reaction. An adverse event triggers the creation of ICSRS (Individual Case Safety Reports), which are then further processed for signal detection and analysis, which can trigger referrals or Periodic Safety Update Report (PSUR) updates. All these assessment and review cascades result in different actions, such as Risk Management Plan (RMP) updates, Direct Healthcare Professional Communication (DHPC) / Educational Material (EM) creation or safety variations. Audits are represented as an umbrella covering all topics, as all PV processes are subject to regular audits in order to detect shortcomings and improve PV systems and processes accordingly. Of course, processes and tasks shown in Figure 1 are not performed serially – this is just a simplified illustration.

Finally, chapter 3 of this thesis highlights the challenges related to these visualised processes for industry as presented in the previously mentioned series of papers, then discusses their positions and proposals, and concludes by identifying redundancies as well as simplification potentials. They are summarised in a table at the end of each chapter.

1.2 Summary of PV legislation in Europe and its evolution over the past decade

The first PV related requirements introduced in 1995 [2] were rudimentary compared to today but legislation has become increasingly complex in the past decade. This chapter briefly describes the reasons behind these legislative changes as well as the consequences for all involved stakeholders.

The new PV legislation became effective in 2012 including significant changes for the pharmaceutical industry, but also for agencies, HCPs (Health Care Professionals) and patients [3]. The primary cause for the extension and further development of PV legislation in Europe was the observation of many deaths due to adverse reactions from medicinal products [3]. This led to a further development of the PV landscape in terms of new laws, definitions, reporting rules, documentation needs, evaluation processes, risk minimisation measures and much more [4]. The European Commission started with an evaluation of the European PV system in 2005 and many initiatives were started during the following years [3]. The result was an adaptation of the existing Directive 2001/83/EC [5] and Regulation 726/2004 [6], hereinafter referred to as “DIR” and “REG”, in December 2010 with significant changes regarding the safety monitoring of a medicinal product throughout the European Union (EU) [2] [3]. DIR 2001/83/EC was amended by DIR 2010/84/EC and REG 726/2004 [3] by REG 1235/2010. The legislation is supported by an Implementing Regulation IR 520/2012 [7], hereinafter referred to as “IR”, that came into effect in June 2012 and is a legally binding act reflecting the performance of PV activities [2] [3]. In October 2012, the PV legislation was updated again due to the review of the medicinal product Mediator containing benfluorex [3]. The product was already withdrawn from some markets in the early 2000s due to the detection of severe safety concerns [8]. Although such measures had already been taken in some countries, the question arises why these withdrawals did not trigger further evaluation of the case on European level in order to evaluate if appropriate action must also be taken in other countries. The legislation in force at the time did not mandate a notification to agencies if an MAH (Marketing Authorisation Holder) took “voluntary” action, such as the withdrawal of a product form the market [8]. The aim of the revision of legislation in 2012 was therefore to further improve patient safety with IR 1027/2012 (effective since June 2013) and DIR 2012/26/EC (effective since October 2013) ensuring prompt notification and assessment of safety issues [3]. In the specific case of the medicinal product Mediator, an Article 107 referral was triggered immediately in order to evaluate whether the safety concerns also applied to all other benfluorex-containing products and in the end the EMA concluded that the benefits no longer outweigh the risks and that all licenses have to be revoked [9].While European Regulations are directly

binding to all member states, an EU Directive must be translated into national law to be implemented, an example being the Medicinal Products Act (German: Arzneimittelgesetz "AMG") in Germany [10]. In addition to the above-mentioned legislation, practical guidance is also provided which is published in accordance with the respective legislation. This guidance is referred to as the Good Pharmacovigilance Practice (GVP) and consists of 12 modules, focusing on the major PV processes. Some of these 12 modules also includes an addendum, providing further detailed information. Additional support is also offered by GVP annex I, which lists all applicable definitions, GVP annex II which provides templates for PSURs and DHPC tasks, GVP annex III which contains other specific PV guidance, GVP annex IV which outlines the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) requirements for PV and finally GVP annex V which summarises all abbreviations. The GVP guidelines also consist of product- or population-specific considerations which are applicable to vaccines, biological medicinal products and the paediatric population. [11]

The aim of the revision of PV legislation was primarily to reduce the number adverse reactions related to the intake of a medicinal product by [3]:

- collecting better data on medicinal products and their safety profile
- rapidly assessing safety issues
- empowering patients through participation in reporting of adverse events
- increasing transparency and communication between all stakeholders
- clarifying roles and responsibilities of MAHs
- reducing duplicate work
- freeing up resources by simplifying reporting rules for safety issues
- establishing a clear legal framework for post-authorisation monitoring

The following paragraphs describe the major changes of the legislation, focusing on those topics which are discussed during the further course of this master thesis.
The fine tuning of the PSUR and RMP rules, resulted in a better collection of key data for medicinal products. Since 2012, all marketing authorisation applications (MAAs) must include a RMP [2, p. section 6.3] and single assessments of PSURS (PSUSA) have been implemented [12]. In addition, the PSUR repository was launched in January 2015 and serves as a central platform for all PSUR-related information [12].
Another new aspect of the legislative revision addresses the adverse drug reaction reporting, which now can be supported by patients [12]. The legislation also provides a new definition of the term "adverse reaction" which in consequence makes it necessary

to also report adverse events which occurred in case of over-dosing, misuse, abuse or medication error. [2, p. section 6.1]

In order to better analyse and understand the data for a medicinal product, signal detection has also been strengthened. According to article 18 of IR 520/2012 [7], all stakeholders (EMA, NCAs (National Competent Authorities) and MAHs) are obliged to continuously monitor the data in the EV (EudraVigilance) database [7]. For this reason, the EV system has been improved and the EMA launched the new version of the system in November 2017. Enhanced functions for reporting and analysis of adverse events are available in order to ensure a better monitoring of the drug. [12]

The updated legislation also led to a change in EMA committees and decision-making processes since the PRAC (Pharmacovigilance Risk Assessment Committee) was established in July 2012 dealing with any PV related topic on European Level. As mentioned before, the referral procedures also strengthen the handling of emerging safety issues (ESI) by introducing the “article 107i” referral. [12]

To improve the communication with stakeholders such as the patients, HCPs and pharmacists, the new legislation introduces a coordinated process for risk communication, such as the DHPC. [12]

Looking at the extensive changes in PV legislation in 2012, it becomes clear that despite many improvements, the pharmaceutical industry was forced to adopt many additional processes and activities leading to a significant increase in workload and complexity compared to the time prior to 2012.

2 Current PV hot topics from an industry perspective

2.1 Reporting of adverse events

One of the most important PV topics for industry is the management of adverse events, as this provides the basic data for the continuous monitoring of the benefit-risk-ratio of a medicinal product. To ensure a safe and effective use of the product, the Marketing Authorisation Holder (MAH) must ensure the close monitoring of the product after authorisation. However, not only the MAH is responsible for reporting adverse events as also HCPs (doctors and pharmacists) and patients contribute to an improved assessment of the benefit-risk-ratio of a medicinal product. The legal basis for this topic is laid down in DIR 2001/83/EC [5] article 107 and article 107a, paragraph 63c AMG [10], REG 726/2004 [6] article 28 and IR 520/2010 [7] chapter V. In addition, GVP Module VI [13] addresses the collection, management and submission of reports of adverse events related to medicinal products.

Adverse events which occur during the use of a medicinal product can be either product-related or non-product related. Until it can be demonstrated that there is no causal relationship between the adverse event and the medicinal product, the case must be treated as a potential suspected adverse event related to the product [13, p. chapter VI.A.1.1]. The MAH is obliged to collect, manage and process these reports to monitor the safety profile of the medicinal product on the market and to update related safety information for the HCPs and the patients [5, pp. Article 107, 107a].

All activities related to the collection and reporting of adverse events from an MAH perspective are roughly outlined in Figure 2.

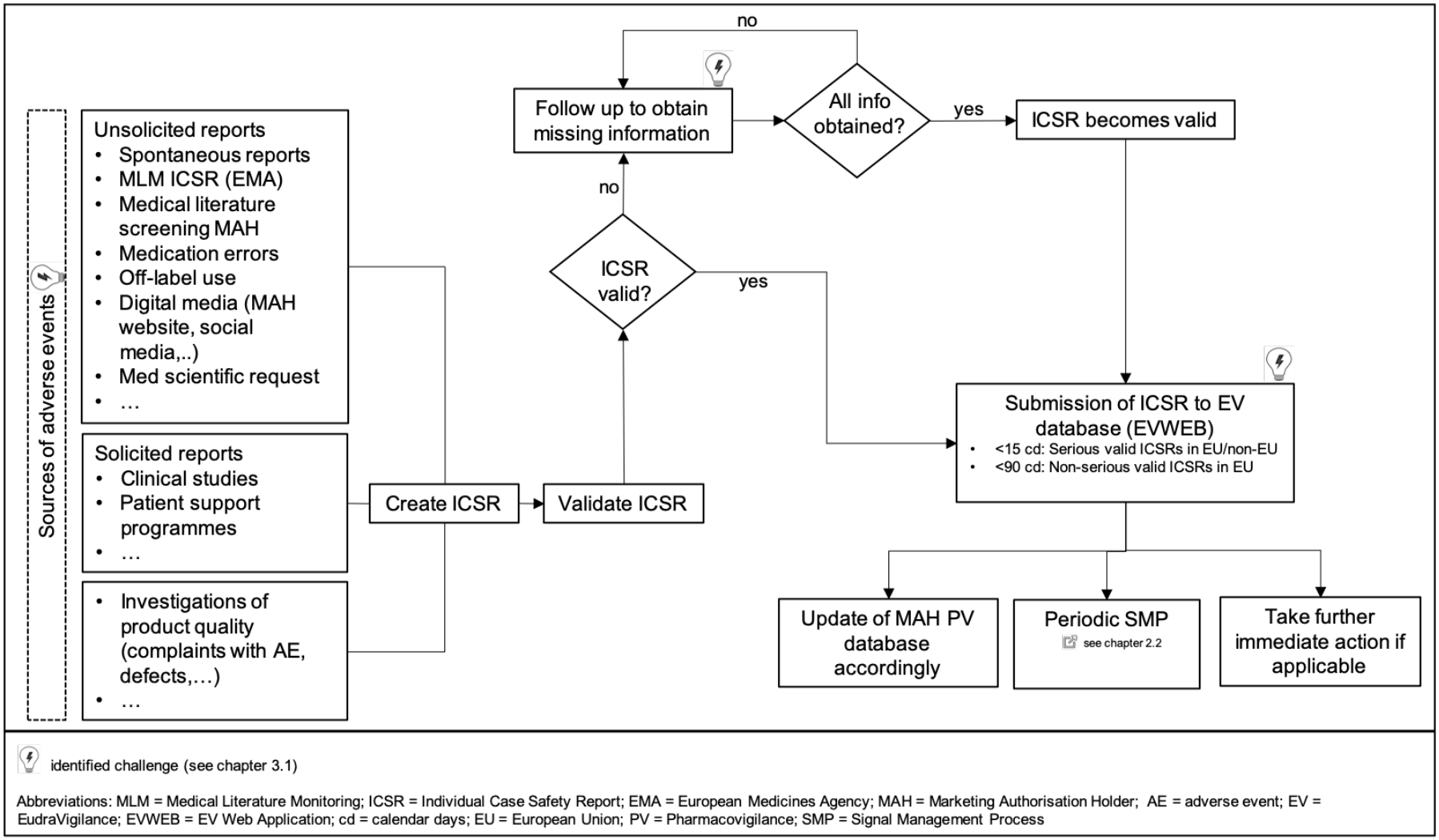

Figure 2: Adverse event collection and reporting process for MAH
(own representation based on [1] [5] [6] [7] [13])

As shown in Figure 2, there are several sources for adverse events. The list in the figure is not exhaustive and is intended to give an overview of potential event sources. In practice, “spontaneous reports” are the main source of adverse events that can be triggered by HCPs or patients. In addition, medical literature monitoring (MLM) reports are an important source, followed by medication errors, off-label use, events popping up in any digital media channel and medical scientific requests which are typically sent to the medical department of a pharmaceutical company by HCPs. However, clinical studies or patient support programmes as well as product quality investigations and complaints can also be a source of adverse events and thus trigger the cascade of ICSR creation [13, p. Chapter VI.B.1].

As soon as an adverse event is reported to the MAH through any of these sources, an ICSR must be created which must meet the four minimal criteria of information: the medicinal product under investigation, an identifiable reporter, an identifiable patient and an adverse reaction [13, p. Chapter VI.A.1.7]. Before the ICSR can be submitted to the EV database for sharing with all stakeholders on European level, the MAH must validate the ICSR, meaning that the minimal criteria must be available [13, p. VI.B.2]. If the ICSR is not valid, the MAH has to perform a follow-up conversation with the reporter [13, p. VI.B.3]. If however the ICSR is valid, it must be submitted to the EV database [6, p. article 24]. The law foresees specific deadlines for the electronic submission of an ICSR, depending on the type of ICSR, i.e. 15 calendar days for all serious ICSRs within the EU and outside the EU, and 90 calendar days for all non-serious ICSRs within the EU [5, p. article 107a (4)]. Following this activity, the MAH updates his internal PV database according to the process defined in the SOP (Standard Operating Procedure) and takes further immediate action if necessary, such as updating the product information texts with a new adverse reaction or adjusted frequency of use. (according to AMG [10] paragraph 11 (1) & 11a (1) in conjunction with AMG [10] paragraph 25 (10), DIR 2001/83/EC [5] article 23 (3), REG 726/2004 [6] article 16(3) and IR 520/2010 [7] article 11 (1 f)). In specific cases, adverse events can trigger referrals (according to DIR 2001/83/EC [5] article 31& article 107i and REG 726/2004 [6] article 20).

As highlighted in Figure 2, the output of this process, i.e. the uploaded ICSRs, is an input to the “signal management process” (SMP) described in chapter 2.2.

The challenges identified by industry related to the activities shown in Figure 2 are discussed in chapter 3.1.

2.2 Signal Management Process (SMP)

The management of signals is one of the core PV activities as it provides the opportunity to identify a potential new relationship between an adverse event and the medicinal product, thus leading to an updated benefit-risk ratio. The aim of a signal management process is to detect potential signals, to assess whether these signals are new or changed risks in relation to the intake of the medicinal product and to consequently define appropriate regulatory measures to minimize these risks [14, p. IX.A.1].The legal basis for this topic derives from DIR 2001/83/EC [5] article 107h, AMG [10] paragraph 63b REG 726/2004 [6] article 28a and IR 520/2010 [7] article 2,11 and articles 19-21. In addition, GVP Module IX [14] addresses signal management and provides clear instructions how to handle this process.

Looking at the big picture of PV activities, the signal management process is not a standalone activity but is well embedded in the entire network of PV processes. As explained in the previous chapter, there are multiple sources of adverse events that trigger the creation of an ICSR, which in is again the input for the signal management process.

All signal management related activities from an MAH perspective are roughly outlined in Figure 3.

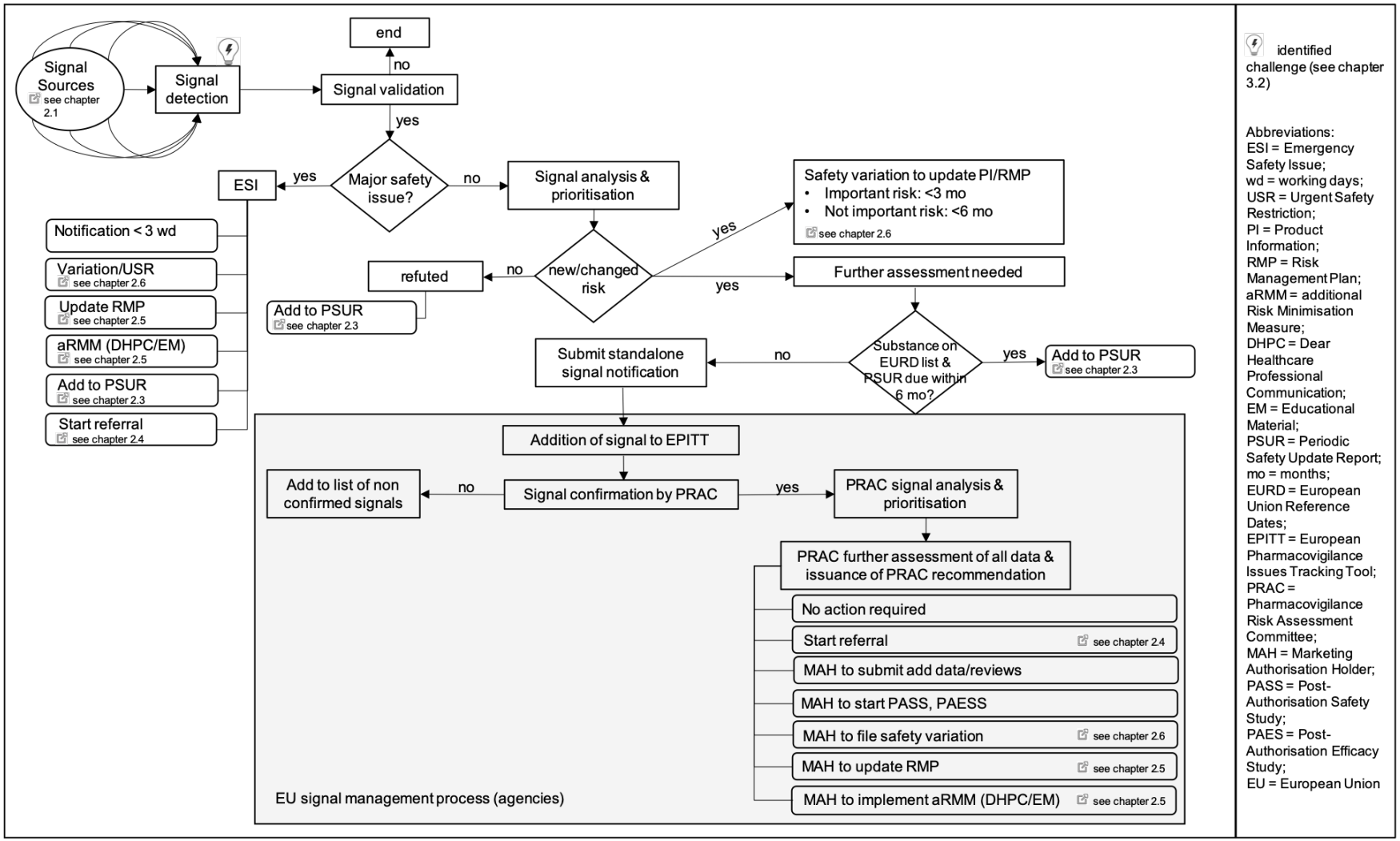

Figure 3: Signal management process for MAH
(own representation based on [1] [5] [6] [7] [14])

The starting point in Figure 3 is the signal source, which can be the MAH's ICSR database or ICSRs in the EV database (see chapter 2.1 for details on sources). The structure of the process is roughly divided into the following segments: "signal detection", "signal validation", "signal analysis and prioritisation", "signal assessment" and "recommendation for action" [7, p. article 21(1)].

During the signal detection phase the MAH identifies a signal through periodic monitoring of the EV database using EVDAS (EudraVigilance data analysis system), which is a component of the EV database [5, p. article 107h(1)]. The detection process should follow a methodology and include statistical methods to analyse the data obtained [14, p. IX.B.2]. After a potential signal is identified, the signal must be validated to confirm or refute that a potential causal relationship with the medicinal product is given. If there is no causal relationship to the product, the process ends at this stage and the result is properly documented. [14, p. IX.B.3] If the signal turns out to be valid, the next step is to evaluate whether it fulfils the definition of a "major safety issue" or not. If a major safety issue is identified, immediate action must be taken by the MAH, which means the submission of a notification to EMA within 3 working days. In addition, appropriate actions and temporary measures are defined in close coordination with authorities. This could, for example, be the submission of a variation to update the SmPC/PIL (Summary of Product Characteristics/Patient Information Leaflet), an urgent safety restriction, the start of a referral, the addition of the signal to the PSUR, an urgent implementation of an additional risk minimisation measure (aRMM) (e.g. DHPC or EM) or the update of the RMP. [14, p. IX.C.2]

If no major safety issue is identified, the signal is further analysed and prioritised. At this stage, the MAH evaluates whether the signal can pose a potential risk to the patient and if not, the signal is listed in the PSUR as "refuted signal". If the analysis concludes that the potential new/changed risk can pose a risk to the patient, it is prioritised according to the risk impact and must be treated according to its risk category ("important risk" or "non-important risk"). In case no further assessment is required, the MAH takes appropriate regulatory action to update the SmPC/PIL to mitigate the risk by e.g. adding warning statements or adapting handling instructions. [14, pp. IX.B.3, IX.B.4] For important risks, this must be completed within 3 months and for non-important risk within 6 months [14, p. IX.C.4.1]. If further assessment is needed, support is provided by the PRAC (EMA's PV committee) which coordinates the signal management process on a European level. Regardless of signals processed by the MAH, the PRAC validates,

analyses and confirms all occurring signals. The PRAC signal management process is also triggered should the MAH signal needs further analysis:

- If the substance is on the EURD (European Union Reference Dates) list and the next PSUR is due within 6 months, the signal is added to the PSUR. This triggers PRAC review during the PSUR assessment. [14, p. IX.C.4.2]
- If the substance is not on the EURD list and the next PSUR is not due within the next 6 months, the MAH must submit a standalone notification to the agency, which triggers a PRAC review of the signal [14, p. IX.C.4.3].

The PRAC refutes or confirms the signal, whereas in the latter case the PRAC further analyses and prioritizes the signal within 30 days of receipt [14, p. IX.C.5]. The PRAC closes the process with the publication of an assessment report that provides recommendations for action. This report is then circulated to all stakeholders involved to take appropriate actions. [14, p. IX.C.6]

As shown in Figure 3, the implementation measures can range from starting a referral, submitting further MAH data for analysis, performing a PASS/PAES (Post-Authorisation Safety Study /Post-Authorisation Efficacy Study), preparing of a safety variation, updating the RMP or implementing a recommended additional RMM (e.g. DHPC or EM). As visualised in Figure 3 this process is linked to many other PV processes and tools and therefore functions as input for them (references are stated in the chart).

The challenges identified by industry related to the processes shown in Figure 3 are discussed in chapter 3.2.

2.3 Periodic Safety Update Reports (PSURs)

Periodic safety update reports (PSURs) are reports which aim to periodically review the benefit-risk ratio of the medicinal product and to identify the need for additional measures to minimize certain risks [15, p. VII.B.2]. The legal basis for this topic is derives from DIR 2001/83/EC [5] article 107b,107c, 107d, 107e, 107g, AMG [10] paragraph 63d, REG 726/2004 [6] article 25a and article 28 and IR 520/2010 [7] chapter VII and Annex II. In addition, GVP Module VII [15] addresses this topic and provides clear instructions how to handle this process.

Before authorisation of the medicinal product the MAH is obliged to collect adequate amounts of data and information about the product related to the core areas quality, efficacy and safety which indicate a specific benefit-risk ratio. Since the data collected before authorisation is limited to a small population, it is important to closely observe the product and its related events continuously during its life cycle after authorisation. A key tool to fulfil this requirement is the creation and maintenance of a PSUR, which is reviewed on a European level at defined time intervals. The PSUR presents all relevant data, arising from the signal management process or other PV sources and comprehensively analyses the risk-benefit balance of the medicinal product [15, p. VII.B.1]. The MAH should critically discuss and review the new available information in the report and outline the identification of potential new risks or changes to already known risks.

Looking at the big picture of PV activities, the PSUR is not a standalone activity but is well embedded in the entire network of PV processes. A variety of PV processes can lead to an update of the PSUR, such as the identification of signals, new risks or updated risks during the signal management process (please refer to chapter 2.2 for more details). The inputs and outputs of the PSUR process are represented in Figure 4 and should give an overview on the critical parameters that flow into the PSUR document and the possible outcomes and consequences of a PSUR review.

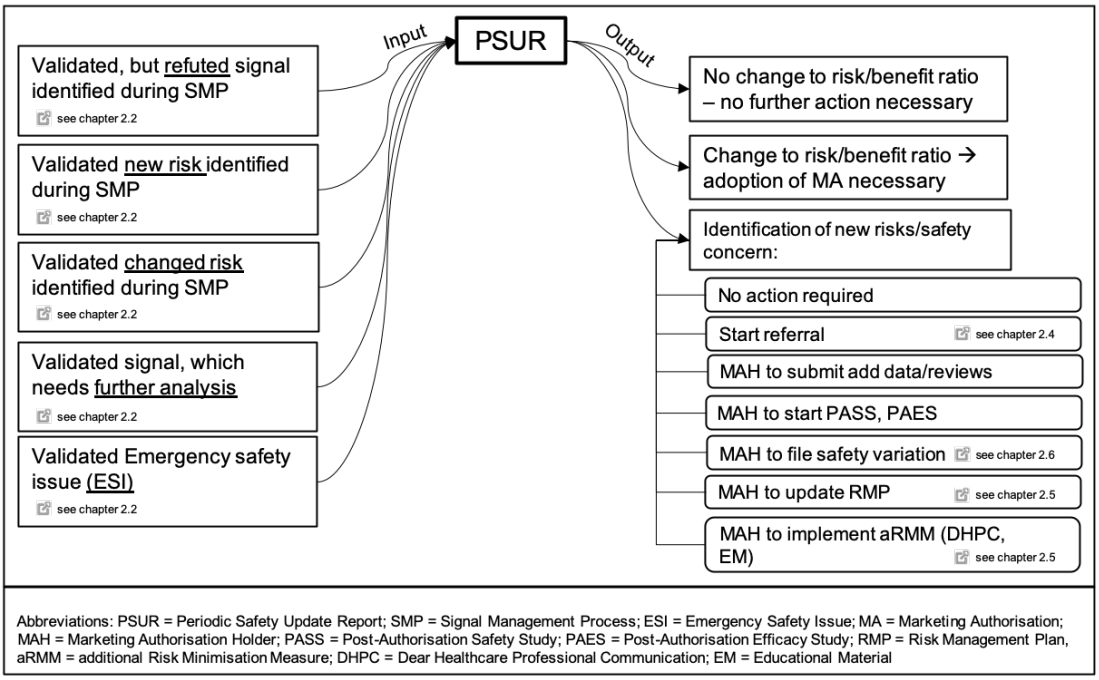

Figure 4: PSUR Inputs & Outputs
(own representation based on [1] [5] [6] [7] [15])

As can be seen in Figure 4, only validated signals are discussed in the PSUR which are those that have a causal relationship to the medicinal product. The outcome or consequences of a PSUR review can vary from no change in risk-benefit ratio, which means that no further action must be taken, to the identification of new risks or an update to already identified risks, in which case the risk-benefit ratio changes and thus may trigger activities, such as the start of a referral (please refer to chapter 2.4 for more details), the submission of additional data by the MAH, the initiation of a post-authorisation study, the submission of a safety variation to e.g. adjust the product information (PI) texts (please refer to chapter 2.6 for more details), the update of the RMP or the implementation of aRMM (please refer to chapter 2.5 for more details).

All PSUR related activities from an MAH perspective are roughly outlined in Figure 5.

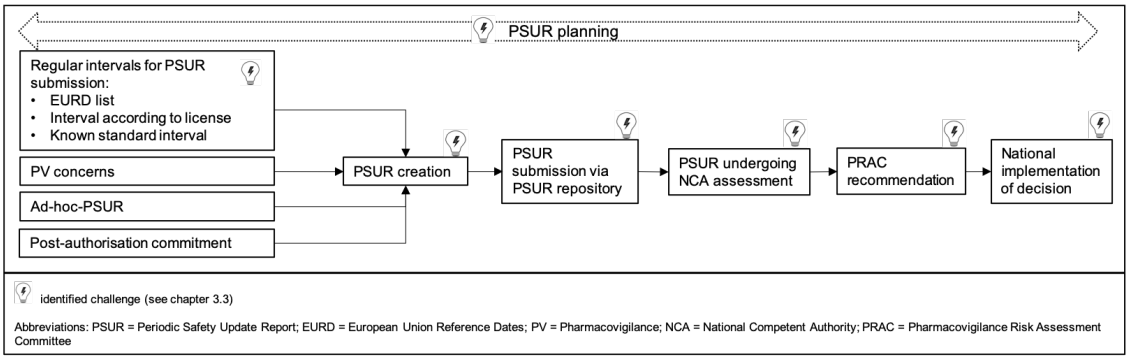

Figure 5: PSUR process for MAH
(own representation based on [1] [5] [6] [7] [15])

As can be seen from the process chart, the MAH needs to accomplish various steps starting with the PSUR creation and ending with the implementation of an EC decision [15, p. VII.C.1]. There are various triggers for creating a PSUR, which can either be regular intervals for PSUR submission or arising PV concerns, ad-hoc PSURS and post-authorisation commitments. The regular intervals may arise from different scenarios: if the product is on the EURD list, the MAH needs to watch it for publications of specific submission frequencies and dates for the substances. If the substance is not on the EURD list, the PSUR reporting interval is either specified in the license documents or underlies the statuary frequency according to DIR 2001/8/EC article 107c [5]. The structure of a PSUR is defined in Annex II of IR 520/2010 [7, p. article 35] and respective detailed guidance is given in GVP Module VII [15, p. VII.B] which will not be discussed further during the course of this thesis.

Once the PSUR is created the MAH submits the PSUR package in order to trigger the PSUR assessment process performed by the agency. In the past, this process was a stand-alone procedure for every single PSUR which lead to a high time and resource investment for the agencies. In the meantime, the process has been simplified, called PSUSA (PSUR single assessment), where all medicinal products with the same active substance from all MAHs are reviewed in one procedure, led by one member state (PSUR-Reference Member State (RMS)). [15, p. VII.C.4.2.2]. Simplification was also achieved through the implementation of the PSUR repository, which is a European PSUR database and the eSubmission Gateway which can be used by the MAH to submit the package. [1, pp. chapter 6, section 1.3] The PRAC is performing the assessment of the PSUR in close alignment with the lead-RMS and issues a PRAC recommendation at the end of the procedure, which outlines recommendation for implementing actions [15, p. VII.C.4.2.2].

The challenges identified by industry related to the activities shown in Figure 5 are discussed in chapter 3.3.

2.4 Referrals

Referrals are procedures on European level, which are “referred” to EMA to conduct a harmonized assessment by EMA’s committee the PRAC and decision for issues such as safety concerns. The legal basis for this topic derives from DIR 2001/83/EC [5] article 29(4), article 30, article 31, article 107i, AMG [10] paragraph 25b (5), paragraph 30 (1a) & (2a) sentence 1 & (3) and paragraph 63e, REG 726/2004 [6] article 20 and IR520/2012 article 13. In addition, the notice to applicants Volume 2A chapter 3 [16] addresses the different types of referrals and provides clear instructions how to handle these procedures.

The thesis will only concentrate on the PV related referral types which are the “union interest referral”, hereinafter referred to as “article 31 referral”, and the “urgent union procedure”, hereinafter referred to as “article 107i referral” [16, p. 3] and will not explain the details of these procedures, as this would exceed the scope of this thesis. The focus will be on the activities resulting for the MAH and to put them into context with the other PV topics presented in this thesis.

Looking at the big picture of PV activities, a referral is not a standalone activity but is well embedded in the entire network of PV processes. The inputs and outputs of a referral procedure are represented in Figure 6 and should give an overview on the critical parameters that trigger a referral and the possible outcomes and consequences of a referral procedure.

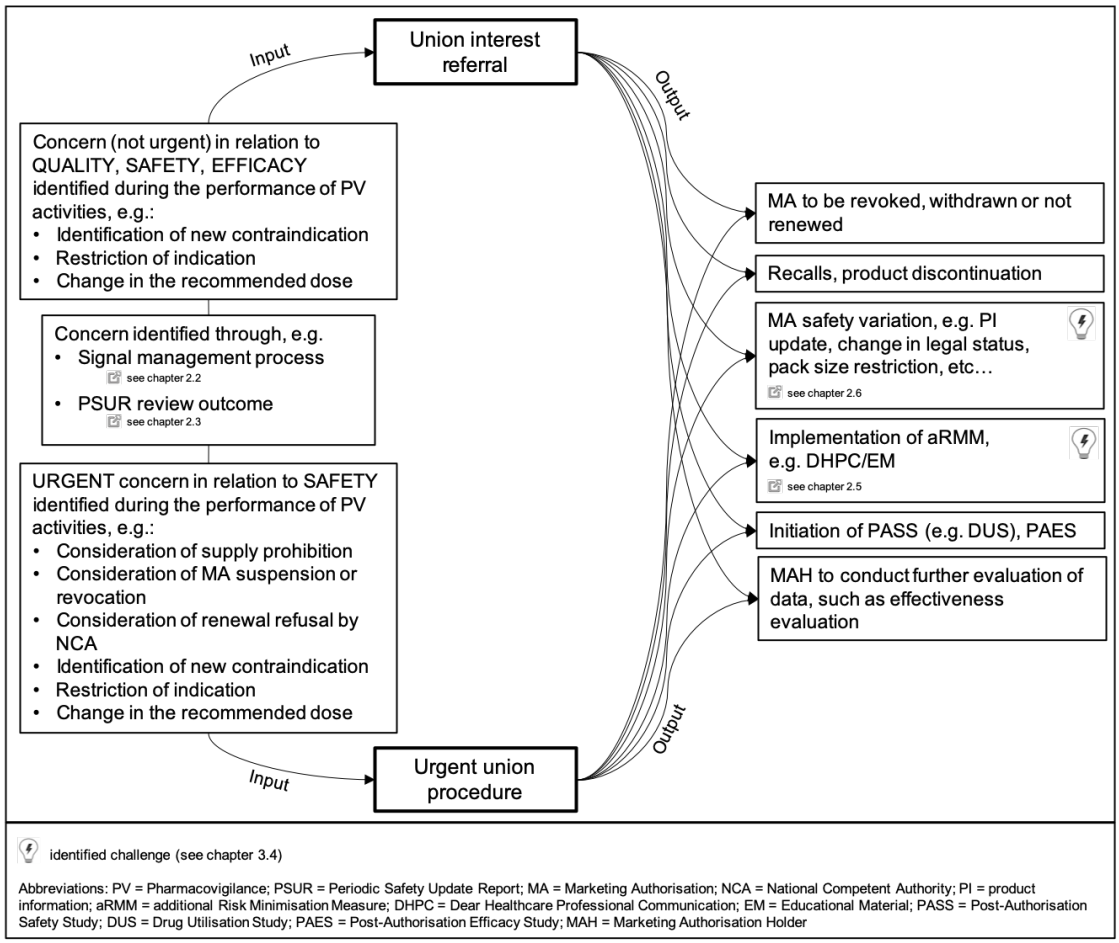

Figure 6: Referrals Inputs & Outputs
(own representation based on [1] [5] [6] [16])

As visualised in Figure 6, the article 31 referral may result from the evaluation of pharmacovigilance data gained during other PV activities, such as from the signal management process as outlined in chapter 2.2 and from the PSUR assessment process as described in chapter 2.3 where a quality, safety or efficacy issue was identified [16, p. 4.1]. Potential reasons may be the identification of a new contraindication, the need to restrict an indication and a change in recommended dose. Where urgent action needs to be taken resulting from evaluation of PV data during other PV activities, an article 107i referral is initiated. Potential reasons could be the consideration of supply prohibition, suspension or revocation of the MA, refusal of the renewal of an MA, supply interruption initiated by the MAH on the basis of safety concerns or the decision by the MAH to withdraw or not renew the MA (Marketing Authorisation) of the medicinal product, but also the identification of a new contraindication, the need to restrict an indication and a change in recommended dose [16, p. 5.1].

During these two referral procedures, temporary measures can be taken at any time during the procedure [16, p. 8]. Depending on the referral type there are is a specific procedure defined including a set timetable, which will not be further discussed in this thesis [16, p. 9]. The referral procedure concludes with a PRAC recommendation which may include one or a combination of the following conclusions. In the worst case the MA is revoked, suspended or not renewed, and in case the medicinal product is not safe for further use the MAH must perform a recall from the market, including product discontinuation. If the referral concludes with the necessity to update the product information texts in order to e.g. update the indication and/or contraindication information or to change the instructions on the recommended dose, the PRAC specifies the exact wording in English and attaches it to the recommendation (please refer to chapter 2.6 for more details). Sometimes restricting measures such as the change in legal status or a smaller pack size are recommended in order to minimize or eliminate a potential risk. Another conclusion can be the implementation of an additional RMM, such as the distribution of a DHPC or education material in order to communicate and minimize certain risks (please refer to chapter 2.5 for more details). In this case, the PRAC also specifies the measures in detail, e.g. the wording of the DHPC or EM, to make sure all MAHs affected have clear guidance what to implement. The initiation of a PASS by the MAH can be also demanded by the PRAC. Sometimes further evaluation of data is needed in the context of the referral procedure. [16, p. 9.4.1]

The challenges identified by industry related to the referral activities are discussed in chapter 3.4.

2.5 Risk Management Plan (RMP) & additional risk minimisation measures (aRMM)

The Risk Management Plan (RMP) is an essential tool to ensure the safe use of a medicinal product. The legal basis for this topic derives from DIR 2001/83/EC [5] article 1, article 8(3)(iaa), article 22c, article 104 (3) & (e), article 104a, article 106 (c), article 107j (3), article 107k, AMG [10] paragraph 4 (36) & (37), paragraph 62 and paragraph 63b, REG 726/2004 [6] article 6(1), article 9(4)(c), (ca), (cb), (cc), article 10a(1), article 14a, article 15, article 21, article 26 and article 28a and IR 520/2010 [7] chapter V and Annex I. In addition, GVP Module V [17] addresses this topic and provides clear instructions how to handle this process.

Since the major revision of PV legislation in 2012, the MAH is obliged to submit an RMP with the application for marketing authorisation [5, p. article 8(3)(iaa)] in order to outline the identified risks associated with the intake of the drug. As outlined in chapter 2.1, the intake of a medicinal product can be associated with adverse events. However, the intake of a drug can never be completely free of risks, therefore it is essential to identify as many risks as possible before the authorisation of the product - but also to continuously monitor the risk profile during the lifecycle of the product, to characterize them and to minimize or prevent the risks by implementing appropriate measures [7, pp. article 30 (1) (a)-(c)]. If the MAH markets multiple products with the same active substance, one common RMP is sufficient [7, p. article 30(2)]. The format of an RMP is also described in more detail in the legislation [7, p. Annex I] and practical guidance is given in the GVP module [17], which will not be discussed further during the course of this thesis. Each time the RMP is updated, it must be submitted to the NCA for review [7, p. article 32 (1)].

The RMP is not a stand-alone document or PV instrument as it is in constant interaction with other PV systems and processes. In order to be able to grasp the full extent of an RMP and its associated activities, it must be seen in the context of the larger PV network. The inputs and outputs of an RMP are represented in Figure 7 and provides an overview of critical parameters which trigger an RMP update.

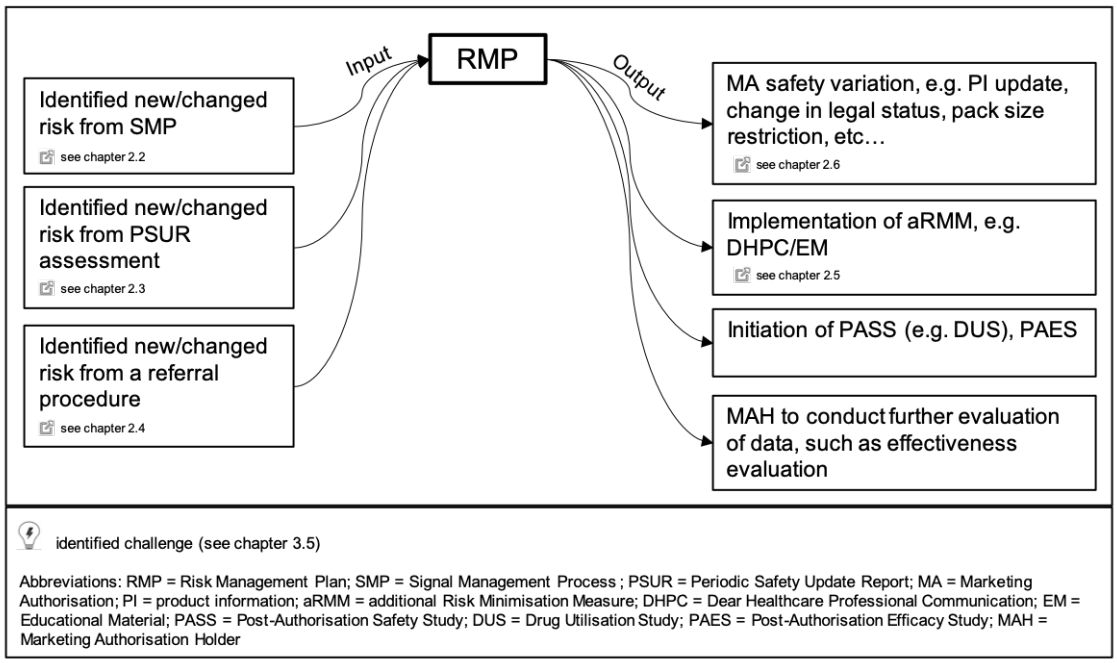

Figure 7: RMP Inputs & Outputs
(own representation based on [1] [5] [6] [7] [17])

The main triggers for an RMP update are “identified new/changed risks” which most often result from the signal management process as outlined in chapter 2.2, from a PSUR assessment as described in chapter 2.3 or from a referral procedure as discussed in chapter 2.4. This again emphasises the importance of event reporting processed and highlighted as potential signals, as this is the only way to identify new risks and thus initiate this critical process to take appropriate risk minimisation measures.

The update of an RMP can have several consequences, which are referred to as “routine risk minimisation measures” (rRMM) such as the submission of a safety variation to update the SmPC/PIL/labelling with additional warning statements, recommendations or handling/dosing instructions, to limit the intake of the drug and to prevent overdosing by providing smaller pack sizes or to reduce the risk associated with the drug and to guard against misuse by change in prescription type (change in legal status, e.g. OTC (over the counter) to Rx (prescription only medicinal product)). Another outcome of an RMP update could be the definition and implementation of aRMM, such as DHPCs or EM, which are discussed in more detail later. [17, p. V.B.8.] Apart from these two aRMM, there are others, such as controlled access programmes, pregnancy prevention programmes, etc. [18, p. XVI.B.] which would exceed the scope of this master thesis and thus are not discussed further. Another consequence of identified new/changes risks could be the obligation to conduct post-authorisation studies (e.g. PASS or PAES) in order to gain additional data on the safety or efficacy profile of the drug, which are

documented in the RMP [7, p. article 30 (1) (d)]. The last possible outcome of an RMP update listed in Figure 7 is the collection of further data by the MAH, such as an effectiveness evaluation.

The above-mentioned rRMM and aRMM shall undergo an effectiveness assessment [7, p. article 30 (1) (c)]. In case the measures turn out to be ineffective or to be a burden to the patients or HCPs, an alternative RMM shall be identified if possible [17, p. V.B.8.].

The PSUR and RMP are the main sources for post-authorisation safety surveillance and risk-benefit assessment and thus overlap in some areas. The main difference can be summarised as follows: the RMP is prospective as it tries to look into the future before a safety issue arises and is a document that is created before the authorisation and is continuously reviewed and updated after the authorisation. In contrast, the PSUR is retrospective because it collects, summarises and discusses all potential signals, validated signals and identified new/changed risks during the lifecycle of the product and is a post-authorisation tool. [17, p. V.B.11.]

All RMP related activities from an MAH perspective are roughly outlined in Figure 8.

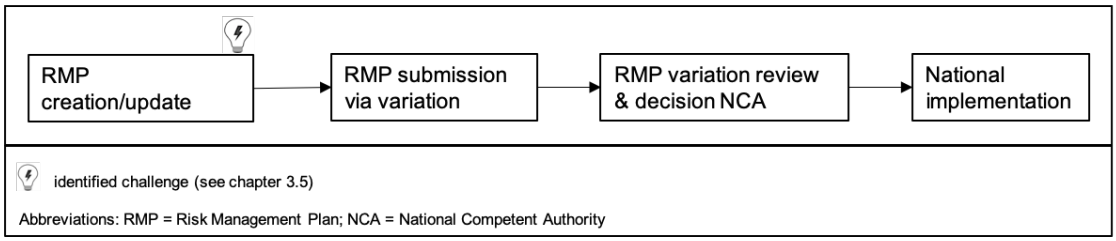

Figure 8: RMP process for MAH
(own representation based on [1] [5] [6] [7] [17])

For marketing authorisation applications before 26 October 2012, the MAH was not obliged to submit an RMP. In this case, a new RMP must be submitted with the next renewal application or at any time upon authority request [17, p. V.B.2.]. To update the RMP, the MAH has to submit a standalone type II variation in accordance with the variation classification guideline [19, p. C.I.11 b)]. The assessment of the application is reviewed by the PRAC for centrally authorised products and the NCA for nationally approved products [17, p. V.C.3].

The challenges identified by industry related to the activities shown in Figure 8 are discussed in chapter 3.5.

Safety Communication

As stated above, one aRMM for an identified risk can be a safety communication. The legal basis derives from DIR 2001/83/EC [5] article 106a [5], AMG [10] paragraph 11a (2), paragraph 62ff and paragraph 63b (2), paragraph 62 and paragraph 63b. The associated GVP source is module XV including Annex II dealing with the details of safety communication [20] and module XVI, which describes in general risk minimisation tools and effectiveness indicators [18].

Various tools are available for safety communication [20, p. XV.B.5.]. Discussing all of them in this thesis would go beyond its scope, thus only the DHPC tool is discussed in more detail as it has been identified by the industry as a challenging process.

The main objective of a DHPC is to provide the HCP with immediate and proactive safety information, including clear and precise instructions on how to take a specific action or to adapt their practices [20, p. XV.B.5.1] to minimize the newly identified risk related to a medicinal product. In Germany, such a letter is called “Rote-Hand-Brief” (RHB), with a logo representing a red hand incorporating the text “important information”. The RHB and the logo was introduced by the BPI 1969 and has become an official tool, which is also used by other associations [1, pp. chapter 9, section 1.2].

All DHPC related activities from an MAH perspective are roughly outlined in Figure 9.

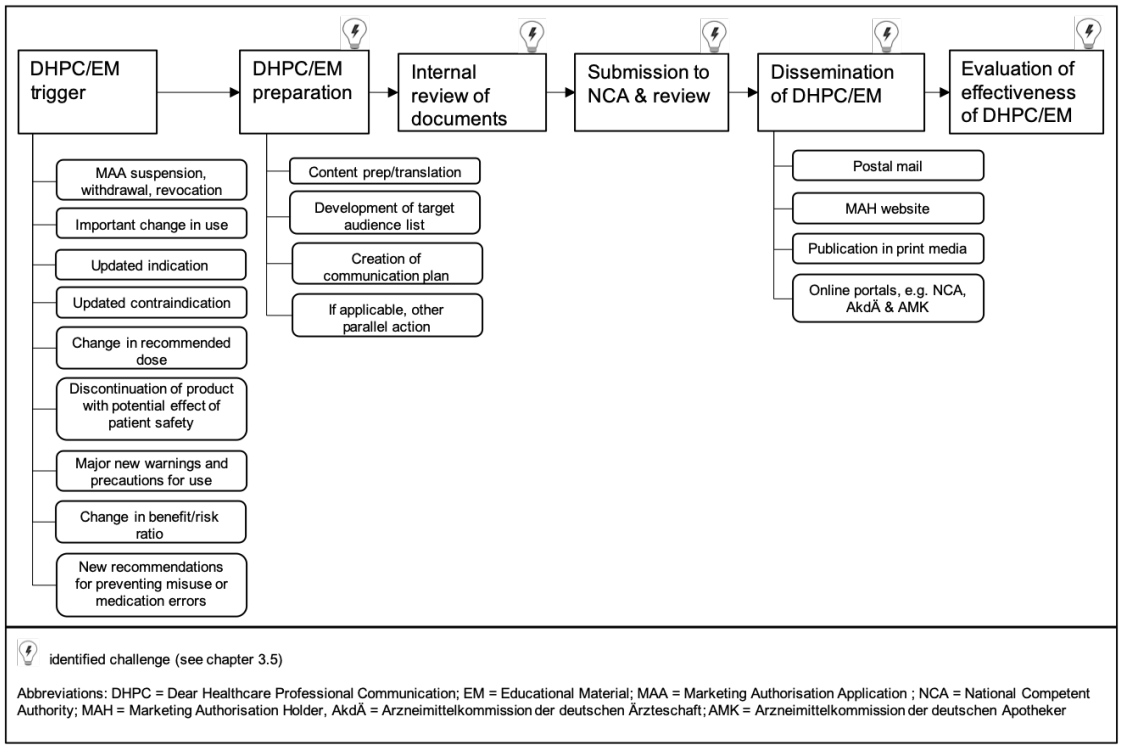

Figure 9: DHPC & EM process for MAH
(own representation based on [1] [5] [6] [7] [20] [21])

There are various triggers for the creation of a DHPC as listed in Figure 9 which can be a result from the signal management process as outlined in chapter 2.2, from a PSUR assessment as described in chapter 2.3 or from a referral procedure as discussed in chapter 2.4. In addition to creating or translating the content, the preparation step includes activities such as the development of an audience target list to narrow down the recipients and a communication plan to define what to communicate and when [20, p. XV.B.5.1.]. Once the letter has been prepared, the MAH initiates an internal review which is conducted by various departments, such as Medical Affairs, Pharmacovigilance or Regulatory Affairs (RA). Once the letter passed the internal review, the MAH is obliged according to the law [5, p. article 106a] to submit the letter to the NCA in order to agree on the content, audience target list and the communication plan [20, p. XV.C.1.1.]. Finally, the letter is disseminated to the target audience. The most preferred distribution way is still physical distribution via postal mail. In addition, other channels such as the publication on the MAH website, online portals from other operators (e.g. NCA, Drug Commission of the German Medical Association (AkdÄ), Federal Union of German Associations of Pharmacists (AMK)) or other print media or can be used [1, pp. Chapter 9, section 1.5].

In case more than one MAH is affected by the safety communication, the originator is informed and will act as the lead in coordinating the content and details between all stakeholders. Industry associations, such as the BPI in Germany, fulfil an essential mediating and coordinating role, not only supporting content coordination, but also managing recipient lists, mailing distribution lists, receiving printing and distribution offers from the vendors and coordinating the invoicing and shipping of printed material to the MAHs. The costs can be split between the MAHs in such a case. [1, pp. Chapter 9, section 1.6]

In order to evaluate the effectiveness of the DHPC, the MAH should implement a respective tool, by defining process and outcome indicators, to assess if there is an added value to the recipients [18, p. XVI.B.4.].

The challenges identified by industry related to the activities shown in Figure 9 are discussed in chapter 3.5.

Educational Material (EM)

As stated above, another aRMM for an identified risk could be the creation of EM for patients, HCPs and pharmacists. It is intended to complement the SmPC and PIL, inform the reader about particularly important risks and give clear instructions. The legal basis derives from DIR 2001/83/EC [5] article 104, AMG [10] paragraph 28 (3a) & (3b) and paragraph 63b and REG 726/2004 [6] article 21. The respective GVP source is module XVI Addendum I [21] dealing with the details of EM and module XVI, which describes in general risk minimisation tools and effectiveness indicators [18].

Since December 2016, NCA-approved EM must be marked with the “blue hand” logo, which holds the imprint “authority approved education material” [1, pp. chapter 9, section 2]. The need to provide education material can be either agreed during the marketing authorisation process (no marketing of the product unless EM has been released to the recipients) or during the lifecycle of a product any time there is a safety concern or need to create EM as aRMM [21, p. XVI. Add I.2.]. The process for the creation and distribution of EM for the MAH is equivalent to the one for the DHPC, so please see Figure 9 for more details.

2.6 Maintenance of licenses

With the approval of a medicinal product, the actual maintenance work begins for companies. The legal basis for this topic derives from DIR 2001/83/EC [5] article 23 (3), AMG [10] paragraph 11 (1) sentence 9 and paragraph 11a (1) sentence 8, REG 726/2004 [6] article 16 (2) and IR 520/2010 [7] article 11 (1) (f). According to these paragraphs, the MAH shall ensure that the product information texts, thus the SmPC, PIL and the labelling (inner and outer carton labels, etc.), are up to date with current scientific understanding, including results, conclusions and recommendations published by authorities or the scientific literature. The MAH is obliged to regularly check the literature and the information on agencies' websites for new information related to the medicinal product and to pursue a risk-based approach to assess whether and how quickly changes to the product information texts are necessary [1, p. chapter 10]. The changes to the product information are based on the legal requirements outlined in REG 1234/2008 [22], which deals with the examination of variations to the marketing authorisation. In addition to this regulation, the European Commission has published a guideline on variation categories in order to support MAH in the classification of variations and to provide procedural guidance [19]. The maintenance of a license does not only include changes to the product information texts, but also to the entire dossier on the approval was based, including quality, pre-clinical, clinical study information. However, this thesis only discusses PV related topics.

Looking at the big picture of the PV activities, the maintenance of licenses processes is not a standalone activity but is embedded in the entire network of PV processes. A variety of these PV processes can lead to an update of the license, such as the signal management process as outlined in chapter 2.2, from a PSUR assessment as described in chapter 2.3, from a referral procedure as discussed in chapter 2.4 or from an RMP update as highlighted in chapter 2.5.

All maintenance related activities from an MAH perspective are roughly outlined in Figure 10.

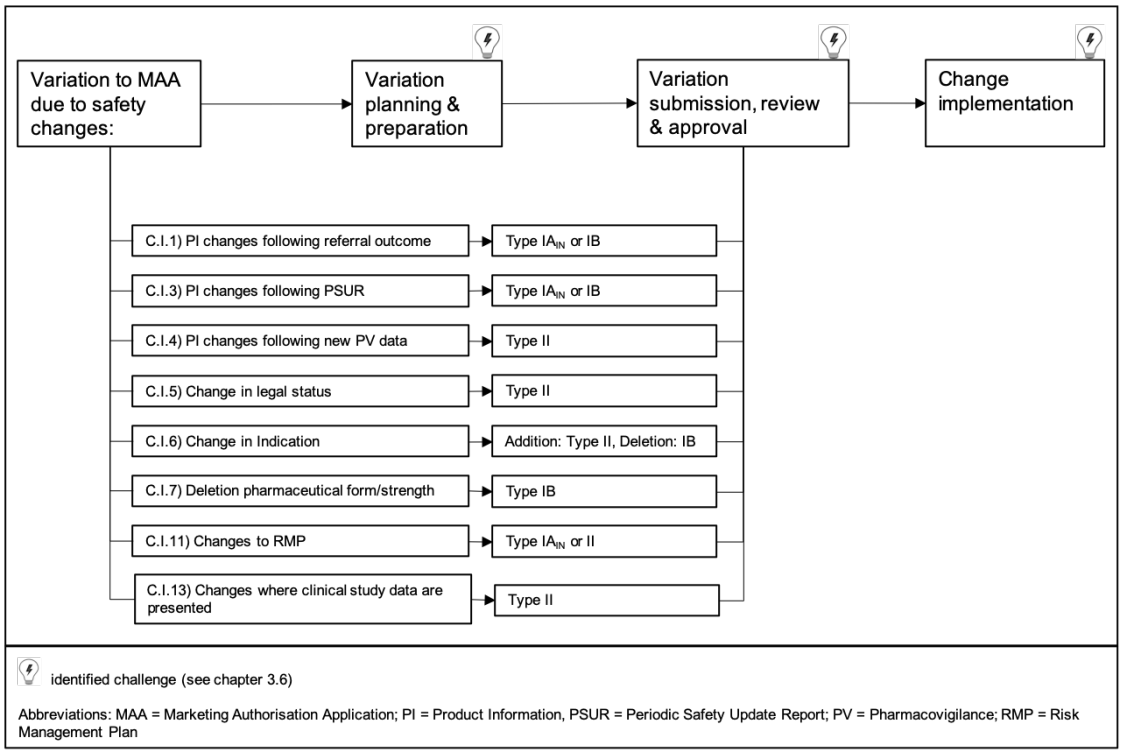

Figure 10: Variation process for MAH
(own representation based on [1] [5] [6] [7] [19] [22])

There are many PV-related triggers for a variation, which are listed in Figure 10.
Variation category C.I.1 refers to changes in the product information texts following a referral procedure [19]. As mentioned earlier in chapter 2.4, the PRAC can conclude with the recommendation to update the product information texts. The wording is provided by the PRAC in English and the coordination of the translation into the EU languages is accomplished by EMA. Since the wording is provided by the agencies and does not require further scientific assessment, the variation type is most commonly a type IA_{IN}. However, practice has shown that in many cases consequential changes to other text paragraphs are necessary, which leads to an upgrade to a type IB variation that requires NCA review. In such a case, the MAH will face higher costs and longer lead time for the implementation of the change. MAHs with products that are excluded from the referral can decide to voluntarily adjust the product information texts to the PRAC wording, which triggers a type IB variation. This ensures an evaluation by the authority whether it makes sense to voluntarily change the product information texts. [1, pp. chapter 10, section 2]
Category C.I.3 relates to changes in the product information texts followed by a PSUR assessment as mentioned earlier in chapter 2.3. The wording is also provided in English and translated into national languages by the agencies and can therefore be filed as type IA_{IN} (IN = immediate notification) variation in most cases. [1, pp. chapter 10, section 2]

Category C.I.4 covers changes of the product information texts due to new PV data. Since new data always requires a scientific assessment by the agency, the variation is classified as type II variation with a review period of 60 to 90 days. In most cases the changes are related to risk or warning statements for the safe use of the medicinal product. [1, pp. chapter 10, section 2]

As mentioned earlier in chapter 2.5 a possible risk minimisation measure to deal with an identified risk, e.g. the risk of overdosing, is to change the legal status of a medicinal product to limit the access and the frequency of use. This can be accomplished with a type II variation under the category C.I.5. [1, pp. chapter 10, section 2]

Sometimes it is necessary to adjust the indication of a medicinal product, for example as a consequence of a referral procedure (please see chapter 2.4 for more details), which can be handled as type II (addition of indication) or type IB (deletion of indication) variation under category C.I.6. Also, the deletion of a pharmaceutical form or strength is handled as type IB variation under category C.I.7. [1, pp. chapter 10, section 2]

As discussed in chapter 2.5 new or changed risks trigger an update of the RMP which can be handled under category C.I.11 as type IA_{IN} variation, if the wording was agreed upfront with the agency or as type II variation if new data is provided which necessitates scientific review.

The last PV-related variation category that will briefly discussed in this thesis are changes based on study results under category C.I.13. Due to the necessity of a scientific assessment of the data, the variation classified as type II [19].

Once the need for a variation is identified, the MAH must conduct proper planning and preparation of the variation. The planning phase is of utmost importance as the change must be viewed from all angles and an impact assessment must be carried out during a change control. During this impact assessment, the regulatory department assesses the variation category according to the EU variation classification guideline [19], which also provides clear guidance on the data requirements for the submission package.

In general, there are three main types of variations: depending on whether the impact on the quality, efficacy or safety of a medicinal product is minor or significant, a type IA [22, p. article 2 (2)] or type II variation [22, p. article 2(3)] must be filed. In addition, there is a type IB variation, which is chosen when the change is neither classified as a type IA nor a type II variation [22, p. article 2 (5)]. Depending on the variation type costs, the type of data to be submitted and the review period differ. The type IA variation is a so called “do and tell” variation, which means that it can be implemented without prior NCA approval and should be reported to the NCA within a timeframe of 12 months. However, a small number of type IA variations should be notified immediately which are called type IA_{IN}

variations (IN = immediate notification) [19, p. 2.1.]. The type IB variation, is a “tell, wait and do” variation, thus the MAH must wait 30 days before implementation of the change [19, p. 2.2.]. Type II variations require NCA approval before implementation [19, p. 2.3.]. An exceptional variation is the “urgent safety restriction”, which is a temporary change to the license if an event is identified that bears a risk to public health and requires urgent action [22, p. article 22]. The package for the urgent safety restriction is submitted to the authority as soon as possible and if no objections are raised by the agency within 24 hours, the variation is deemed accepted and the MAH can implement the change within the agreed timeframe [19, p. 2.6]. There are also other types such as extensions or cases of unforeseen variations, which are not further discussed in this thesis.
Given the high amount of variations during the life cycle of a product, the administrative burden is immense for both the MAH and the agencies. In order to remedy the situation, simplification initiatives have already been implemented. One is the possibility of grouping variations according to article 7 of REG 1234/2008 [22] where multiple changes can be combined in one variation procedure. Another initiative is the use of a work-sharing procedure according to article 20 of REG 1234/2008 [22] which allows to combine one change for multiple licenses in one procedure. The details of these initiatives would exceed the scope of this thesis; thus, they are not discussed further.

As shown in Figure 10 after the planning and preparation phase of the variation, the MAH submits the package to the NCA for review and approval. The review timelines for the assessment and the timepoint of implementation of the change differ depending on the variation type [22].

After approval of the variation, the change can be implemented via multiple tasks such as the update of internal databases, internal communication of updated product information texts, closing of change control tasks, upload of new product information texts in NCA databases and on the MAH website and finally, but most important, the update of artwork.

The challenges identified by industry related to the activities shown in Figure 10 are discussed in chapter 3.6.

2.7 Pharmacovigilance Audits

As mentioned in the introductory note of this thesis, the PV requirements have increased immensely since the new PV legislation was introduced in July 2012, with audits were a significant part of this revision. Their main objective is to assess the pharmacovigilance system in order to identify weaknesses.
The legal basis for this topic derives from DIR 2001/83/EC [5] article 101(2) and article 104 (2), AMG [10] paragraph 63b (2), REG 726/2004 [6] article 21 (3) and IR 520/2010 [7] article 13(1) and article 17(1). In addition, GVP Module IV [23] addresses this topic and provides clear instructions how to handle this process.

The MAH is obliged to perform risk-based audits at regular intervals in order to assess the appropriateness and effectiveness of the pharmacovigilance system [7, p. article 13 (1)] and to define corrective and follow-up actions as necessary [7, p. article 13 (2)]. The interval shall not be longer than five years [23, p. IV.B.2.]. An audit is a systematic, documented and independent process that leads to an objective assessment to which extent the audit criteria are fulfilled [23, p. IV.B.1.]. There are various ways an audit can be performed, however they are not further discussed in this thesis.

This topic presents a special challenge for industry, as in many cases the company cannot maintain PV presence in every country and has to rely on partners/contractors. Increasingly, the growing regulatory requirements related to audits and the expectations of authorities are no longer manageable for companies as resource investment is enormous and audit quality cannot be adequately met. Often, the audit isn't actually applicable or appropriate in a specific setting. As the number of required audits is growing constantly, the industry has developed strategies to plan, prepare, execute and follow-up on audits. [1, p. chapter 12]

All audit related activities from an MAH perspective are roughly outlined in Figure 11.

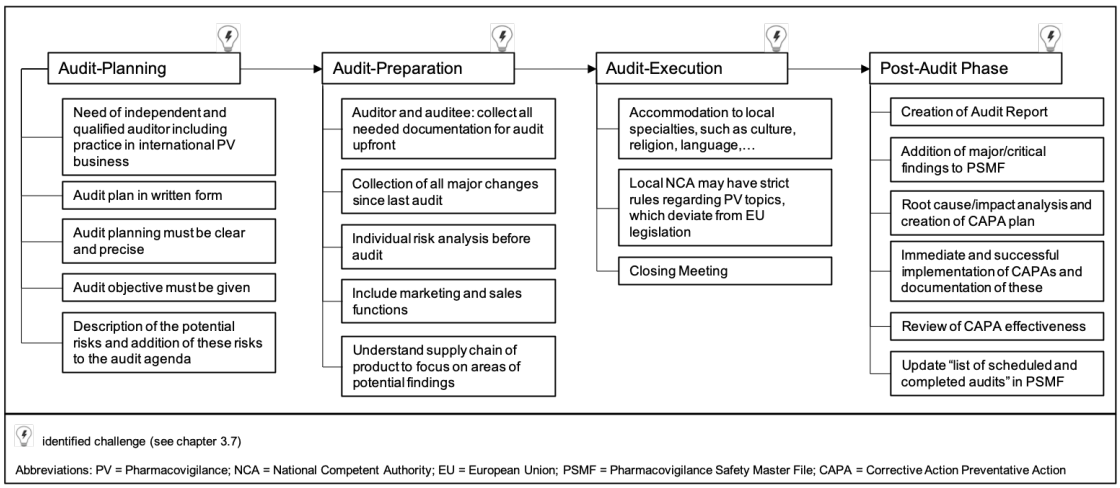

Figure 11: Audit process for MAH
(own representation based on [1] [5] [6] [7] [23])

The planning phase of an audit is a critical stage at which the frame of an audit is determined. The first important requirement is that the auditor is qualified and independent and has experience in international PV business [1, pp. chapter 12, section 4] in order to ensure a professional and quality-assured execution of the audit. The audit planning should be performed in written form. The respective audit plan must be written in clear and precise language and must contain the scope of the audit and its associated risks [23, p. IV.B.1.]. An audit agenda is created, which includes all topics for discussion and which respects the time difference, possible language barriers and, if applicable, religious aspects [1, pp. chapter 12, section 4]

The preparation phase deals with the collection of all necessary documentation and thorough understanding of the processes and structures involved in the audit. It is beneficial to review all major changes within the company in terms of resources, processes and other critical parameters. All parameters which may impact the patient's safety are particularly relevant and should be analysed before the audit in order to identify potential weak points. This individual risk analysis allows to reduce the time required for the audit as much as possible. It is also beneficial to include other functions such as marketing and sales. Local particularities are also a significant factor during an audit in a global environment. [1, pp. chapter 12, section 4]
After successful preparation, the audit is executed. For audits abroad, it is important to accommodate to local characteristics such as culture, language and religion. Local authorities may have different legislation compared to the EU, which can lead to deviations in processes and activities. It is essential to have a closing meeting on the last day in order to summarise all discussed points and findings. This meeting should

also provide the opportunity to clarify any remaining questions. [1, pp. chapter 12, section 4]

The post-audit phase is again very time consuming as the audit report must be prepared with detailed information on topics discussed and the identified findings. All critical and major findings must be added to the PSMF (Pharmacovigilance Safety Master File). The PSMF also contains a list of completed and scheduled audits, which needs to be updated after each audit. The findings must be removed as soon as possible, including a root cause analysis in order to understand the source of the error. A corresponding CAPA (Corrective Action Preventative Action) plan is compiled to remove the deficiencies and to prevent them from recurring. The CAPA effectiveness shall also be evaluated. [1, pp. chapter 12, section 4]

As highlighted above, it may not always be possible the companies to audit every PV partner/contractor on-site. In addition to the above-mentioned measures to reduce the resource consumption and to keep the costs down when preforming an on-site audit, companies can introduce remote-audits (web and phone-based audits) or use synergies by performing joint-audits. Due to the high degree of globalisation in the pharmaceutical sector, the acceptance of the use of remote audits is absolutely critical. It avoids travel time and costs; audit dates can be easily adjusted and more frequent audits can be performed for critical partners. However, this type of audit involves a more intensive preparation phase, the necessity to have reliable and efficient IT (Information Technology) systems and clear phone connections and may involve barriers related to cultural difference, languages and missing body language. Time zone differences also play a huge role for remote audits as people involved may be sitting on different continents in different time zones. [1, pp. chapter 12, section 5]

There is another audit type that uses synergies, the joint audits. This can be performed to save time and costs for every party involved when a partner needs to be audited by several companies. This topic is quite new, therefore there are no clear guidelines and the acceptance from an agency's perspective is questionable. Thus, the BPI discussed this topic with the German NCAs in February 2019 and concluded with criteria of acceptance of joint audits, which include the following are amongst others: [1, pp. chapter 12, section 6]

- Multiple MAHs form a consortium and hire an auditee which fulfils the qualification according to GVP module IV B.3.1.2.

- The establishment of a contract between the auditor and the consortium is of utmost importance, reflecting rules of communication for frequent updates and immediate communication of findings
- The results of the audit will be circulated to all MAHs
- A full initial on-site audit must have been performed with the partner/contractor before a switch to a joint audit can be done
- In focus are processes and thus regulatory requirements which are the common denominator for all MAHs involved. All individual topics which need to be address by single MAHs are not in scope for this type of audit and must be handled separately.

The challenges identified by industry related to the activities shown in Figure 11 are discussed in chapter 3.7.

3 Identified challenges and position/demands of industry

3.1 Reporting of adverse events

The legal requirements and the respective PV activities the industry is confronted with related to the reporting of adverse events have been summarised and put in relation to other critical PV processes and tools in chapter 2.1. The aim of this chapter is to highlight identified challenges according to the industry's perspective and to outline possible solutions or proposals/demands as defined by them, in order to simplify the processes and tasks in the complex PV network.

The pharmaceutical industry highlighted the lack of awareness among HCPs and patients about the importance of reporting adverse reactions as a major challenge [1, pp. chapter 1, section 4]. The MAH cannot act correctly and in compliance with the law if adverse reactions are not reported consistently. Thus, the patient and the HCP have a tremendous responsibility for the collection of product related safety data and therefore contribute to the evaluation of a more precise benefit-risk profile of a medicinal product. Although the package leaflet contains information with clear instructions where to report an adverse reaction, this tool is not always used [1, pp. chapter 1, section 2]. In contrast to patients, HCPs are legally obliged to report adverse reactions. Although there is a guideline published by the AkdÄ, which describes in detail why it is so important to report adverse event, what to report and how to report it, some HCPs still show a lack of knowledge and awareness. The AMK also provides guidance for the pharmacists on how to deal with adverse reactions and how to report them. [1, pp. chapter 1, section 3] From an industry point of view, it is therefore essential to further create awareness and support by providing information through various channels such as the AkdÄ and AMK [1, p. chapter 1; section 4]. Another reason why adverse reactions are not reported in some cases, is the misbelief that a reaction that is already listed in the SmPC/PIL does not have to be reported again [1, pp. chapter 1, section 4]. As it is essential to also monitor the frequency of an adverse reaction, all cases must be reported. Because of this issue, industry is still expecting a lot of educational work for themselves and for other institutions. The key is an increase in communication initiatives to better educate and train the HCPs and patients. [1, pp. chapter 1, section 4]

Another major practical challenge for the MAH is the creation of valid ICSR that provides the green light for submission to the EV database. In practice, almost no case is reported with all necessary information, since the reporter often does not know which information should be reported. Another reason can be the constant time pressure that doctors are

exposed to every day. If initially some of the required data is not provided, the MAH has to perform a follow-up with the reporter to obtain the missing information, which represents an additional time investment for the reporter. Although there is clear guidance not to overwhelm the reporter with time consuming activities, the reality is different because of the applicable legal requirements for the MAH. To name just a few, the MAH must immediately perform the follow up, in a way it can be properly documented using a standardised procedure that should cover all eventualities. This leads to over-dimensioned surveys, which necessitates significant time investment by the doctor, who may react stressed or annoyed, which in turn can lead to a reduced reporting rate. Also, sometimes the reporter is not the patient, but the pharmacist. As a result, not all relevant information may be available to the reporter at the time of reporting and therefore remains questionable whether the follow-up conversation is even applicable at this stage. [1, pp. chapter 1, section 4] In any case, the MAH should have the possibility to focus on a compromise between shorter surveys while still complying to regulatory requirements.

Medical scientific requests and complaints are normally directed to the MAH. These involves medical questions about the medicinal product and often include a hidden adverse event. The employees must be trained well to detect these hidden reactions to trigger the creation of an ICSR and thus include these events into the further evaluation processes. [1, pp. chapter 1, section 4]

The fact that one adverse event can be reported from multiple sources to multiple recipients, can lead to redundant reporting pathways. Figure 12 summarises all possible reporting pathways:

- Patient and HCP report the same adverse event to the MAH
- Patient and HCP report same adverse event to the NCA
- The reporter informs the MAH and the NCA for the same adverse event
- Literature reporting for the same adverse event

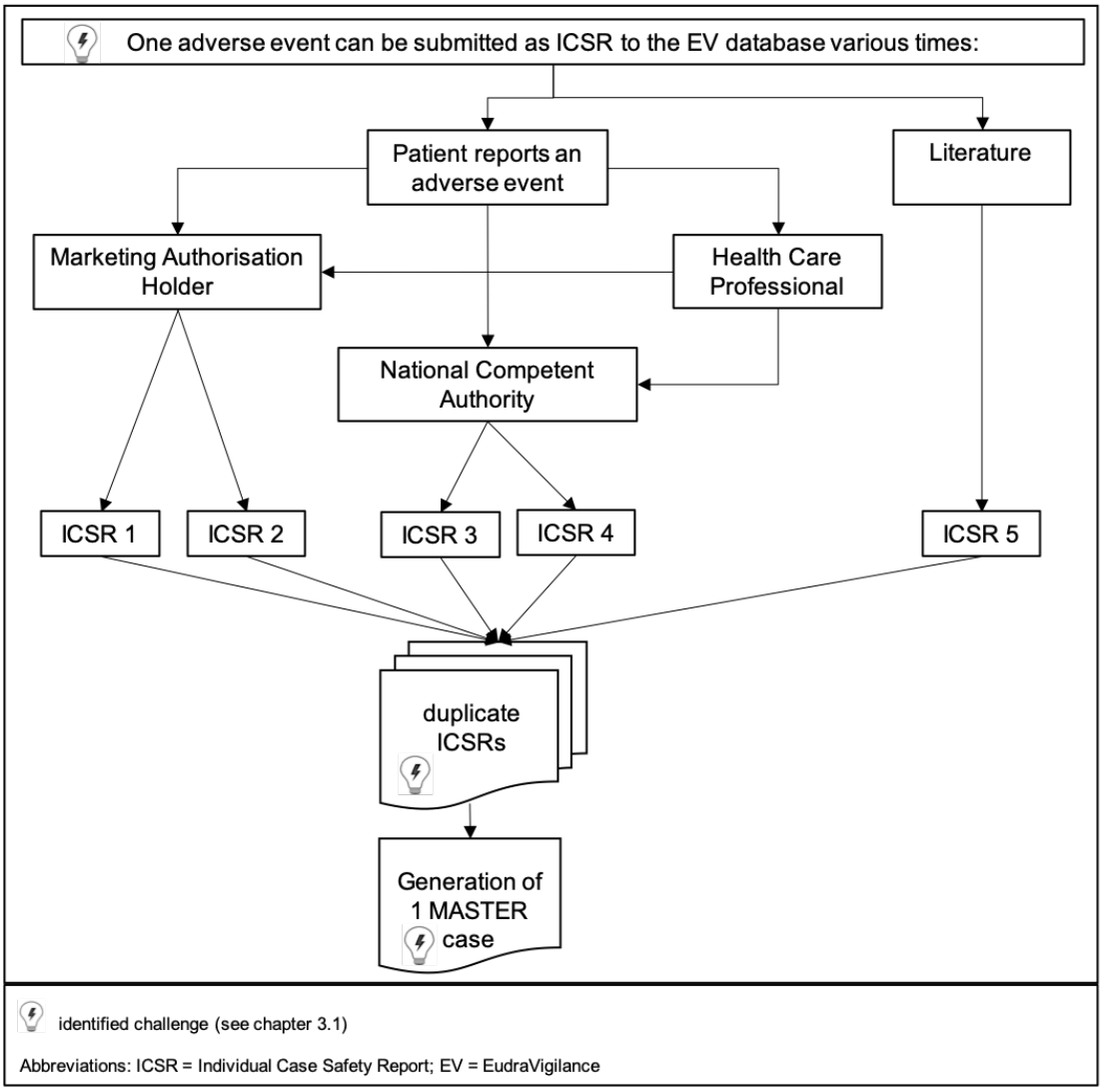

Figure 12: Duplicate ICSRs
(own representation based on [1] [13] [14] [24])

As can be seen in Figure 12, these multiple reporting pathways can lead to the creation of multiple ICSRs. If they are consequently submitted to the EV database, so called "duplicate ICSRs" add up in the system. Such duplicates are considered highly problematic by industry, as they pose a significant problem in the analysis of signals. Duplicates can therefore lead to false results and thus negatively influence the safety evaluation of a product and may set wrong regulatory actions. Some initiatives to reduce the number of duplicates are already underway, for example, the "simplified reporting" initiative. [1, pp. chapter 1, section 4] This new rule reduces the pathway between the MAH and the NCA, because the MAH now reports directly to the new PV database and no longer to the NCA [24, p. VI.Add I.1]. Although initiatives already exist, it is of utmost

importance for the industry to develop even more efficient strategies to avoid duplicates. [1, pp. chapter 1, section 4]

However, duplicates can never be completely eliminated, thus all involved stakeholders must continuously contribute to the detection and elimination of them [5, p. article 107(5) & 107a(3)]. Addendum I of the GVP module VI provides practical guidance dealing with duplicates and explains in detail how these can be properly detected and managed [24]. If duplicates are detected in the system, the technical consequence is to create a master case in which all available information related to the one adverse event is merged into one large case. The master case always represents the most current information and stores all related duplicate ICSRs underneath, so they can always be accessed. [24, p. VI.AddI.3]

Although good guidance is available and several initiatives aim to keep duplicates to a minimum, there are circumstances that lead to duplicates:

- The case narrative is a critical element in an ICSR that provides the background of the case and contains all relevant medical information. In an ideal world, when a new adverse event is reported to the MAH, he screens its own PV database as well as the EV database to determine if the case has already been reported through an alternative pathway. In order to judge whether the exact same case already exists in the system, the “case narrative” is required, since it contains all medical and administrative details about the case. Since the MAH does not have any access to the “case narrative” at the beginning, the MAH cannot outperform a proper evaluation. Only the authority always has full access to all data which is criticised by industry. As the case is entered into the system and can create a duplicate. Therefore, it is a major industry demand to have full access to the data at any time. [1, pp. chapter 2, section 3]
- The reporter checks the EV database for an available ICSR to decide whether the newly received case needs to be added but cannot find it in the database even though it already exists. One possible reason for this is the poor query function in the system. There is currently no query function in the system for master cases and their relating cases, which makes the case selection highly inefficient. The process of identifying and filtering duplicates represents a tremendous burden on resources and time for the MAH and creates additional unnecessary workload when processing data for further use. Industry is demanding to make such a query function accessible as quickly as possible, and while the EMA is currently implementing it, this process is ongoing. [1, pp. chapter 1, section 4]

- Not all reporters may be aware of the avoidance and management of duplicates, thus the industry strongly recommends that the EMA publishes a guidance document related to the management of duplicates. [1, pp. chapter 1, section 4]

Apart from the fact that duplicates should always be avoided the solution to create master cases can be also challenging. Divergent information can be available in the single cases, which makes it difficult to merge the information and decide which information is valid. Apart from that, the task is time consuming. [1, pp. chapter 2, section 3]

Finally, the industry highlighted that the data quality of ICSRs in the EV database may sometimes be poor. Although a set of minimal information must be available to enter the case into the database, poor quality is often found in terms of data consistency, representation of the data and completeness of the entries. The quality of the cases is of utmost importance when it comes to the evaluation of data and to the selection of cases for further data processing. This bears the risk that a potential signal is overseen and may not contribute to the constant re-evaluation of a product's safety profile. The industry insistently suggests to all MAHs to establish internal quality checks of the entered data. This should also be reflected in the internal SOP. To monitor the process, KPIs (Key Performance Indicators) can be defined, which can be measured periodically. Another possible solution outlined by the industry would be the publication of a guideline with specific naming conventions and rules for entering data. This would ensure more consistent data and a better data quality. [1, pp. chapter 3, section 2.1]

The above discussed challenges and possible solutions/ demands from the industry are summarised in Table 1.

Table 1: Summary of challenges related to the collection and reporting of adverse events identified by the industry and positions/demands

identified challenges	position/demands
Reporters	
Lack of knowledge on reporting rules	MAH and other institutions (AkdÄ, AMK) to further educate the reporters
Lack of awareness how important reporting is	Create awareness to every reporter how important his contribution is

identified challenges	position/demands
Misbelief that a reaction that is already listed in PI texts does not need to be reported again	MAH and other institutions (AkdÄ, AMK) to further educate the reporters
Reporters often send incomplete information → long and time-consuming follow-ups are necessary	MAH and other institutions (AkdÄ, AMK) to further educate the reporters on the minimal criteria to be reported
Over-dimensional follow-ups can lead to stress, anger and therefore to bewilderment and annoyance for the reporter	MAH to compromise between shorter surveys and still comply to regulatory requirements
Medical scientific requests and complaints often contains hidden adverse events	MAH to train the employees well to detect such hidden adverse events to trigger ICSR creation
Duplicates	
Duplicates can lead to false results and may therefore negatively influence the safety evaluation of a product and may set wrong regulatory actions	All stakeholders to create even more efficient strategies for avoiding duplicates
Duplicates create significant additional work for the MAH	
Duplicates are often not recognised in the EV database	Detection of duplicates should be simplified
Missing case narratives can lead to the creation of duplicates	MAH to have full access
Poor query functions in the EV database can lead to the creation of duplicates	Agency to improve query function
Rules for managing duplicates might not be understood by all stakeholders	EMA to provide guidance document related to the management of duplicates
Creation of master cases is not trivial (conflicting information in the ICSRs)	
EV database	
Poor data quality of the reports can lead to overlooking signals → leads in the worst case to a wrong safety profile of the medicinal product	1) MAHs to establish internal quality checks of the data 2) MAHs to define KPIs to measure the quality of data periodically 3) Agency to define a naming conventions and rules for data entry

3.2 Signal Management Process (SMP)

The legal requirements and the respective PV activities the industry is confronted with related to signal management have been summarised and put in relation to other critical PV processes and tools in chapter 2.2. The aim of this chapter is to highlight identified challenges according to the industry's perspective and to outline possible solutions or proposals/demands as defined by them in order to simplify the processes and tasks in the complex PV network.

Companies using the component EVDAS for signal detection, face a lot of challenges. Currently, there is no legal obligation to use this tool, nonetheless companies are advised to. The industry highlighted some of the challenges:

- The use of the system requires specific training. EMA provides a lot of online training where guidance is given, e.g. how to retrieve eRMRs (electronic Reaction Monitoring Reports). This ties up resources within the company and requires trained personnel. [1, pp. chapter 3, section 2.1]
- An EVDAS screening process must defined and built into the MAH's internal PV processes. The process should be designed in a way to cover all regulatory requirements while being limited to a reasonable amount of work. Especially small and medium sized enterprises are barely able to handle the associated workload. The industry suggests an "optional-mandatory" use of EVDAS. [1, pp. chapter 3, section 2.1]
- eRMRs contain thousands of entries. Since the filter function is very rudimentary and limited to the active substance high level group, the results cannot be narrowed down into a smaller data set. Therefore, the MAH is required to further filter the results in other applications, such as Microsoft Excel, which creates additional workload for the MAH. An industry proposal to EMA is to define additional mandatory fields, e.g. route of administration, pharmaceutical form or indication for which a filter function is available. [1, pp. chapter 3, section 2.1]
- Poor data quality of the ICSRs in the EV database complicate the screening process (please refer to chapter 3.1 for more details). [1, pp. chapter 3, section 2.1]
- In addition, the ICSR download is limited to a time period of maximum two weeks, which means that the MAH need to run several queries to cover a longer time period. The industry proposes a widening of the query period to save time and resources. [1, pp. chapter 2, section 3.1]

- Due to the restriction if full data access for the MAH, the case narrative is not included in the initial ICSR download. This means that the most critical information for the medical assessment of the case is not available but is needed to identify potential signals. The absence of the case narrative can lead to a wrong medical case assessment and poses the risk that either an important case is not investigated further, or a case with false relevance is included into the signal management process. The industry demands full access rights. [1, pp. chapter 2, section 3.1]
- EMA uses different technical standards for the submission of ICSRs to the database and for the data in the EV database. The technical details are not discussed further in this thesis, but the different data formats often lead to conversion issues and data loss. Industry position is that only one data format should be used and EMA should adapt the systems accordingly. [1, pp. chapter 2, section 3.1]
- As mentioned in chapter 3.1 the duplicates are a major problem in signal detection. The MAH must ensure to eliminate duplicates as efficient as possible before applying the signal detection methods, as this can lead to false signals. The industry proposals on how to reduce duplicates are discussed in chapter 3.1. [1, pp. chapter 2, section 3.3]

General challenges related to signal management communicated by the industry are:

- According to GXP module IX, the term “validated signal” and “non-validated signal” are linked to the fact that a signal validation process has been performed and has led to a result, i.e. a negative result in case of a “non-validated signal” and a positive result in case of a “validated signal”. These definitions are still ambiguous, because they do not exclude the option that validation has not yet been performed. Therefore, the industry proposal is to change the terms to “valid” and “non-valid” signal, as this eliminates the ambiguity. [1, pp. chapter 3, section 3]
- GVP modules V, VII and IX contain different definitions related to signals and risks, since the revision of the modules was not coordinated with one another. This is very confusing and makes it difficult for the MAH to design internal PV processes with a consistent use of these terms. The industry wishes for clarification of the terms and respective revision of the concerned GVP modules by the agency. [1, pp. chapter 3, section 3]

The above discussed challenges and possible solutions/demands from the industry are summarised inTable 2.

Table 2: Summary of challenges related to signal management identified by the industry and positions/demands

identified challenges	position/demands
Signal detection in EVDAS	
System trainings are required, which ties up resources	
The workload associated with EVDAS is significant and difficult for some companies to manage	The use of EVDAS should be "mandatory-optional"
Oversized eRMRs due to the rudimentary filter function → considerable additional workload for MAH	Agency to define additional mandatory fields, e.g. route of administration, pharmaceutical form or indication for filtering
Poor data quality of ICSRs complicates further data screening	Please see chapter 3.1
ICSR download period is limited to a period of 2 weeks → additional workload for MAH	Extension of the query period
Lack of case narrative can lead to false signal detection	MAH to receive full data access
Different technical standards used by EMA for ICSRs can lead to conversion issues and data loss during further processing of the data	Agency to adjust its format and use only one format
Duplicates can lead to false signal detection	Please see chapter 3.1
General aspects	
GVP module IX: terms "validated" and "non-validated" signal are still ambiguous	Use terms "valid" and "non-valid" signals instead
Definitions related to risk and signals are not consistent in GVP modules V, VII and IX	Clarification of terms and respective revision of GVP modules by the agency

3.3 Periodic Safety Update Reports (PSURs)

The legal requirements and the respective PV activities the industry is confronted with related to PSURs have been summarised and put in relation to other critical PV processes and tools in chapter 2.3. The aim of this chapter is to highlight identified challenges according to the industry's perspective and to outline possible solutions or proposals/demands as defined by them in order to simplify the processes and tasks in the complex PV network.

The EURD list needs to be consulted by the MAH at least once a month as substances currently not on the EURD list may be added at any time or published submission dates may change. This activity requires resources and should be incorporated into the MAH's PV processes and reflected in the respective SOP. [1, pp. chapter 6, section 6.1] In case of ad-hoc PSUR reviews, the MAH must be able to provide the necessary resources internally in order to complete the related tasks. This is not plannable for the MAH, thus may often represent a challenge. It is beneficial to calculate the personnel within the company in a way that there is a certain flexibility for such ad-hoc activities.

The creation of a PSUR is not an easy task and requires long-term planning with appropriate margins. In some cases, this task lies within the responsibility of the PV department, but may also be part of RA tasks. However, the company should clearly define this in the respective job descriptions in order to clarify the roles and responsibilities. With regards to the PSUR creation process, the following challenges have been identified by the industry: [1, pp. chapter 6, section 6]

- The MAH needs to provide sufficient resources and know-how to handle this process. Excellent project management skills are needed as cross-departmental collaboration is critical. The industry recommends regular meetings with all stakeholders, in order to keep everyone aware of the deadlines at all times and to also align the content of the PSUR, as the input is gained from multiple departments. This project coordination is exceptionally time-consuming and requires highly developed communication skills. The industry recommends creating a PSUR planning matrix to define the roles and responsibilities for each person and department involved. This helps to define a clear process which can be executed accordingly. For smaller companies it is often challenging to free up resources available for project management. [1, pp. chapter 6, section 6.1]

- In order to avoid redundancies between the PSUR and the RMP the content preparation gets even more complex which again needs more detailed management and alignment. [1, pp. chapter 6, section 7]
- The format requirements of PSURs still differ in some countries, which leads to redundant work for the MAH as multiple documents need to be created and maintained. There has already been some simplification in Switzerland as the Swiss authority accepts EU PSURs for all standard submissions. Also, the PSUR format has been harmonised in EU and US (United States). However, these two examples are still exceptions and a lot of further work required in order to reduce complexity from a global perspective. Industry stresses the necessity of further cooperation between European and Eurasian authorities in order to harmonize PSUR templates to avoid redundant work. The suggestion from the industry is to create user friendly templates which also address the different risk structures of the products on the market. Until some degree of simplification is eventually achieved by the authorities, the MAH should focus on implementing respective strategies and processes to reduce the burden for the departments where possible. [1, pp. chapter 6, section 8]

The submission of the PSUR to the PSUR repository via the eSubmission gateway simplifies some aspects for the MAH, but also bears some challenges:

- Specific and complex IT knowledge is needed in order to access and use the system, which means additional training for the personnel and appropriate IT support within the company. [1, p. chapter 6; section 6.2]
- The submission procedure itself is very time consuming and error-prone, so at least 2-4 weeks should be calculated in the timetable for this task, which is an exceedingly long time. Considering the time-consuming content preparation, the whole PSUR process tends to drag on and become increasingly complex. The industry demands a simplification of the submission process. [1, p. chapter 6; section 6.2]
- As they experienced numerous technical bugs in the past, the industry expresses the need for a technical update to eliminate these bugs. [1, p. chapter 6; section 6.2]
- The file upload is limited to 10 MB (Megabyte), which is problematic in practice as PSURs often exceed this file size. The upload limited should be adjusted to a higher size by the agency. [1, p. chapter 6; section 6.2]

The costs for the PSUR single assessment are borne by the MAH(s) and are currently annotated with 19.500 Euro per procedure [1, pp. chapter 6, section 6]. In case more MAHs are involved in the assessment, the total sum is divided proportionally between them. In case only one MAH needs to pay the fee, it poses an immense cost burden for the company.

The outcome of a PSUSA is most commonly a voluminous report, which contains general parts and parts which do not affect all MAHs. Thus, it is important for the MAH to screen the report as soon it is available for implementation actions and their timelines. [1, pp. chapter 6, section 6.3] It is essential that these actions are communicated internally to all stakeholders as soon as possible in order to plan the tasks accordingly. The activities should be tracked until completed and the regulatory strategy needs to be aligned with the RA department. Again, this activity requires time consuming-project management.

The above discussed challenges and possible solutions/ demands from the industry are summarised in Table 3.

Table 3: Summary of challenges related to PSURs identified by the industry and positions/demands

identified challenges	position/demands
Check EURD list monthly	MAH to incorporate this task into PV processes and internal SOPs
PSUR creation	
Complex process which requires long-term planning and proper project management → high resource investment	
Setting PSUR/RMP boundaries is complex and time consuming	
Different PSUR format requirements in different countries	Further cooperation between the European and Eurasian authorities to harmonize PSUR templates
PSUR submission	
Complex IT knowledge required by MAH	MAH to have proper IT support and training
Time consuming submission procedure for MAH	MAH to plan appropriate buffer and agency to simplify process
Technical bugs → time consuming	Agency to eliminate bugs
Limitation in file size when uploading → technical issues	Agency to adjust file size capacity
PSUR assessment	
PSUR review fees are very high	
PRAC recommendation	
Voluminous report needs to be screened → high workload for MAH	
All actions must be tracked until completion → high workload for MAH	

3.4 Referrals

The legal requirements and the respective PV activities the industry is confronted with related to referrals have been summarised and put in relation to other critical PV processes and tools in chapter 2.4. The aim of this chapter is to highlight identified challenges according to the industry's perspective and to outline possible solutions or proposals/demands as defined by them in order to simplify the processes and tasks in the complex PV network.

A referral can be triggered at any time during the lifecycle of a medicinal product and are unpredictable for the MAH. As outlined in chapter 2.4, any quality, safety or efficacy concern can trigger a referral and may not even occur in connection with the medicinal product in question. Also, PV issues identified for the same medicinal product owned by another MAH or for another medicinal product using the same active substance may trigger a referral which involves all MAHs. Thus, there may be circumstances in which the own medicinal product does not show a safety issue for the moment but will also be included in the referral, as there might be a potential risk of this issue occurring in future. Until a product can be excluded from the list of potentially affected medicines, the MAHs are required to follow the respective referral rules and activities, and function as active participants in this procedure. The cost of a referral is significant, even though the total sum is split between all involved MAHs. In addition, referrals are time intensive, on average taking 15,7 months for an article 31 referral and 6,8 months for an article 107i referral, which means additional strains on the MAH in terms of workload during this phase, as the MAH needs to be in constant contact with the agencies, provide data and to attend meetings [1, pp. chapter 8, section 3]. As referrals occur randomly it is impossible for the MAH to anticipate these costs in the resource and budget planning process and as referral should be always prioritised the MAH faces the risk that other tasks are neglected.

Once the PRAC recommendation is issued, the MAH needs to take immediate action to implement the measures. This step may represent the biggest challenge for industry, as the implementation of the PRAC recommendation is handled on national level, thus by the NCAs [1, pp. chapter 8, section 4]. This may lead to national differences in terms of timelines and content due to divergent interpretations by the NCAs. From an industry's point of view less room for national interpretations would be beneficial [1, pp. chapter 8, section 4]. In the following bullet points, a few challenging situations for the MAH are discussed in more detail:

- Update of product information texts: in case an update to SmPC/PIL/labelling is needed, the PRAC recommendation contains the exact wording which shall be used by all MAHs. This wording is provided in English and translated into local languages of the member states by the NCAs. This step often leads to varying translations due to different interpretations, which leads to differences in wording in the product information texts. As patients or HCPs may be confused by the different wordings, such situations should be avoided as much as possible. The industry wishes for a wording proposal in local language for entire sections or for the entire documents to allow harmonised changes of product information texts on European level. This would save time as well as prevent disharmonised product information texts, contributing to an increase in transparency and safety for the HCPs and patients. [1, pp. chapter 8, section 4.1]
- Classification of variation type for product information text updates: in order to conduct the recommended changes to the product information texts, the MAH must file a respective variation. Therefore, the MAH must evaluate the classification according to the variation guideline. Since the wording is provided by the PRAC, the text changes can be classified as a type IA variation as no further scientific assessment is needed by the NCA. Thus, a pragmatic, rapid and easy implementation is secured. However, in practice, there are serval circumstances where the text changes lead to consequential changes in other paragraphs within the document. In such a case, the variation category is upgraded to a type IB variation, which increases the timelines and costs of the variation. Consequently, the MAH cannot implement the change immediately, which leads to a delay in the publication of important safety information to the HCP and patient, which does not underline the intention of such a measure. [1, pp. chapter 8, section 4.1]
- The variation should be submitted within 10 days after issuance of the commission decision [25, p. 3.1] by the MAH, however, this is handled differently in practice. Once the PRAC recommendation is published, the NCAs send out local notifications to the MAHs reflecting important information regarding the variation type, submission due date and wording in local language. The timelines given are not always identical between the different member states. Some NCAs rely on the 10 days and some set their own timelines, which makes it challenging for the MAH in terms of planning and coordination, as the product is usually marketed in more than one market. This increases the complexity of handling and coordinating all activities and leads to a huge time and resource burden for the MAH. The industry

wishes to have the same implementation dates in all countries to reduce the complexity in the coordination of the tasks. [1, pp. chapter 8, section 4.1]

- Creation of EM: The PRAC recommendation also includes the wording for EM in English in order to assure harmonised EM among the different products. The translation is coordinated by the MAH with the NCAs on national level. This means that each country has its own processes and timelines, which makes it very challenging for the MAH to coordinate all these separated tasks with different local requirements. There are two proposals according to the industry's voice to reduce the burden for the MAH: One would be the coordination of the translations by industry associations, such as the BPI in Germany. This would add value for all MAHs involved and save a lot of time in total. Another option could be that the translation is done by the NCAs in alignment with the PRAC wording, so that the PRAC recommendation already contains a translation. Both proposals would lead to a harmonisation of the content of EM and to a reduction in time, resource and cost burdens for the industry. [1, pp. chapter 8, section 4.2]
- EM publication: the publication of EM underlies also national legislation and is different in every member state. In Germany, the NCA already published a detailed process and checklist how to handle this process which already reduces unclarities, but not all member states have such guidance. The industry wishes for a clear process and guideline in all member states, so that activities can be planned more precisely. This would at least reduce some of the time burden for the MAH, as a lot of time is invested to clarify the procedure and next steps with the NCAs. [1, pp. chapter 8, section 4.2]
- Creation of DHPC content: the same problems as described above for the creation of education material apply to the DHPC creation. The proposal from the industry is to also coordinate the translations via the industry associations and to use their direct connection to the AkdÄ and AMK to distribute the letter. [1, pp. chapter 8, section 4.3]
- Conduction of PASS: if the MAH is obliged to conduct a PASS (e.g. drug utilisation study (DUS)), a huge time, resource and money investment is needed. There is the opportunity to conduct joint studies for all affected MAHs which would reduce the burden for all parties. However joint studies are very problematic as it is hard to find an MAH who voluntarily takes over the lead. Not only because of the costs and resources needed, but also because the process itself is still very unclear. From an industry perspective there should be further clarification in the process and interactions between all stakeholders in order to offer an incentive for the companies to join forces. [1, pp. chapter 8, section 4.4]

The above discussed challenges and possible solutions/ demands from the industry are summarised in Table 4.

Table 4: Summary of challenges related to referrals identified by the industry and positions/demands

identified challenges	position/demands
Medicinal product can be in scope of referral procedure even though the associated risk has not occurred for this product	
High costs of a referral procedure	
Average time of a referral is quite long	
Referral is not plannable for MAH	
Challenges related to the implementing actions of a referral	
Disharmonised wording in PI texts due to different translations and review on national level	Wording proposal in local language for entire section or for the entire document should be provided to the MAH
Variation type often needs to be upgraded from type IA to type IB due to consequential text changes → delay in providing the information to the audience	
Submission due date for variation differs on national level	To agree on the same implementation dates in all countries
Translation of EM is performed at national level → disharmonised text	1) Coordination of the translations by industry associations 2) Translations to be fully prepared by the NCAs in alignment with the PRAC wording
Publication guidelines for EM differ in every country → complex to handle	To provide clear process and guideline in all member states
DHPC translations are complex	Coordination of the translations by industry associations
The process for joint studies is still very rudimentary	Further process clarification is needed and clear interactions between all stakeholders should be defined

3.5 Risk Management Plan (RMP) & additional risk minimisation measures (aRMM)

The legal requirements and the respective PV activities the industry is confronted with related to the RMP and risk minimisation measures have been summarised and put in relation to other critical PV processes and tools in chapter 2.5. The aim of this chapter is to highlight identified challenges according to the industry's perspective and to outline possible solutions or proposals/demands as defined by them in order to simplify the processes and tasks in the complex PV network.

A conscientious handling of risks requires a proactive management and tracking, a responsibility which requires the appropriate resources by companies. Effective and accurate tracking and monitoring tools must be available in order to keep track of all risks. Cross-departmental collaboration between at least Pharmacovigilance, Regulatory Affairs and Medical Affairs is critical and require streamlined and effective communication channels. Regular meetings are important to align all stakeholders on the action items and timelines. All these activities require detailed project management, for which there may not always be enough resources within the company due to its consuming nature. [1, pp. chapter 5, section 8]

The MAH can market the product in several countries, which means that the MAH must be aware of all relevant national RMP requirements, which can vary from country to country. There is no global template for RMPs, therefore the MAH is required to generate multiple RMPs for one product which significantly increases the administrative burden. For industry a globally harmonised RMP template, that can be used for all markets, would be ideal. This would reduce the workload immensely, save time and costs and would free the resources for other critical activities. [1, pp. chapter 5, section 8]

Multiple MAHs can produce the same medicinal product, resulting in the existence of multiple RMPs, which are not aligned as of today. Considering generic products, this can be quite a challenge as the RMP needs to be in line with the originator product. With the availability of multiple disharmonised originator RMPs, it is hard to decide for generic companies on which RMP to lean on. The best approach would of course be to find the small common denominator of all originator RMPs, which is more difficult than expected. [1, pp. chapter 5, section 8] To create simplification, an initiative (project HaRP – "Harmonisation of RMP Project") has already started on European level to harmonise all RMPs for the same product from different MAHs, which aims to publish an RMP template

to use for generic products after the market exclusivity of the originator product has expired. [1, pp. chapter 5, section 7]

Looking at challenges associated with the available guidelines, the industry has identified difficulties in deciding which risk is classified as an “important risk”. The second revision of GVP module V has already remediated and specifies this term as those risks that are likely to affect the benefit-risk profile of the medicinal product [17, p. V.A.1.]. In practice however, it is not always so obvious how to classify a risk. The EMA has already taken the initiative to publish a list of identified important risks to support the MAH in the decision-making process [26]. The MAH should access this list at least weekly to view the updates [1, pp. chapter 5, section 8]. The correct classification is critical, because the measures taken for an important risk can differ from a non-important risk. The timelines and regulatory consequences also differ.

DHPC/EM

The content preparation of the DHPC/EM can be a challenge in practice. The statements and information contained in the material must be precise, correct, simple and especially practical and executable for the HCPs in their daily business. Therefore, the preparation of such an item must be adequately planned, coordinated and tracked. Project management skills are critical and associated free resources must be available. To cope with all related tasks, it is important to set up regular meetings to coordinate and align all stakeholders. Close cross-departmental collaboration, such as Pharmacovigilance, Regulatory Affairs and Medical Affairs is required to create the content and for the internal review cycle of the DHPC/EM. All tasks listed are significantly challenging for the MAH considering, that a company has multiple products on the market. [1, pp. chapter 9, section 4.1 & 4.2]

Furthermore, when an HCP is required, more than one MAH may be affected. In order to avoid overloading the HCPs or patients with redundant information material and prevent the loss of critical safety information, it is important to align the material as much as possible. In case of a DHPC, the best solution is for the companies get together and create one identical letter which is distributed in an aligned and coordinated way. If multiple MAHs are concerned, the lead is normally taken over by the originator company, which communicates with everyone and coordinates all tasks with the involved parties. In addition, the costs of such a measure can easily escalate, because printing and shipping are significant cost factors when addressing a large target audience. The costs can be shared between the involved MAHs, reducing the cost burden for all parties. In

addition to the use of synergies between the participating MAHs, the support of industry associations such as the BPI in Germany, is another effective strategy to reduce the burden on the industry and to simplify the process. They support the coordination of tasks, in the communication with the agencies and with the execution of tasks, as far as possible. [1, pp. chapter 9, section 4.1]

If the DHPC is physically distributed via mail, the letter must first be printed and then disseminated to the target audience. This step takes a few extra days compared to a digital publication of the letter, which needs to be added to the schedule to ensure a timely distribution according to the agreed timelines. Since this is still the preferred way of distributing DHPCs in Germany, most companies need to plan an adequate budget for this step. [1, pp. chapter 9, section 4.1]

The industry also identifies many challenges when it comes to EMs. Apart from the content preparation challenges described above, the MAH is not allowed to market the product unless the EM has been received by the target audience, even though the authority has granted the marketing authorisation. This is essential for industry as the company constantly loses sales every day the product is not on the market due to pending EM. This means, that the process for creating the education material should be started significantly in advance, which has proven to be difficult in practice. The industry cannot directly accelerate the regulatory timelines related to the approval of EM - which may require significant time - and can only focus on keeping the internal review cycles as short as possible. A close and pragmatic collaboration with the NCA is critical to shorten the timelines to a minimum. [1, pp. chapter 9, section 4.2]

If education material is required for a generic product, it should be identical to the originator product. Differences in the EM between an originator and generic product confuse the target audience as this can lead to different or contradicting information. In an ideal world, the MAH of the generic product copies the education material from the originator product. This is currently not possible due to trademark issues under the current legal situation. The industry therefore desires a simplification in this area, which includes harmonised education material templates which can be used for everyone. Generic EM is already implemented for a small number of active substances and is available in multiple languages. This effort could be continued in the future to include even more active substances or medicinal products. [1, pp. chapter 9, section 4.2]

The decision for the need of EM is currently handled on national level, which means that each NCA is independent to impose the creation of such material to the MAH and thus may be inconsistent internationally. This creates an additional uncertainty for companies when launching new products and leads to a considerable additional effort for those countries where EM is required, resulting in a massive cost and resource burden for the companies, additional to all other tasks. According to the industry's position, stronger alignment is necessary on a European level, including the transparent communication of the decision-making processes which lead to EMs by NCAs. [1, pp. chapter 9, section 4.2]

The creation and dissemination of EM is not a one-time activity but a continuous process. It must be constantly updated as soon as changes to the MA occur e.g. the change in dosage or additional warning statements regarding the handling of the product. This means additional maintenance work for the MAH for which resources and time must be available. [1, pp. chapter 9, section 4.2]

A public survey conducted by the AkdÄ in 2016, where the EM of 23 medicinal produces were reviewed, concluded that there was no clear focus on safety concerns – which would have been the primary purpose of the EM and renders it pointless for the HCP. Recently, the quality of EM has improved due to more specific regulatory guidance and available templates. However, there is still a lot of room for improvement that should be addressed by the agencies. In addition, patient interviews have shown that the EM is not always patient-friendly in terms of layout, structure and lay language. Patients want a clear guidance, including reasons, to fully understand the instructions in the EM. Avoiding redundancies between the EM and the SmPC/PIL also facilitates the delivery of required information. For these reasons, industry concluded that EM must be designed in a recipient-specific manner in terms of layout, language and type of instruction. Although this may require additional efforts by companies, it is important not to lose sight of the purpose and significance of EM, as it is rendered useless if the information is not understood by the recipient. [1, pp. chapter 9, section 4.2]

Unfortunately, a lack of awareness of the existence of EM has been identified among the HCPs and patients even though the blue hand logo is printed on the material. The companies and other associations, such as the AkdÄ and the AMK, are called on to increase marketing for the blue hand logo and better communicate the significance of this symbol. It is important to emphasize that EM is not promotional material and only focuses on important, helpful, scientific information. MAHs should also communicate the

concept of the blue hand logo internally to train sales staff and other personnel in contact with HCPs or patients, emphasising to explain the meaning of this symbol whenever possible. A clear message should be passed to the target audience, that EM is a risk minimisation measure complementing the SmPC/PIL and a regulatory condition for the sale of the product. [1, pp. chapter 9, section 4.2]
In theory, EM should be handed to the patient by the HCP, which does not always correspond to reality and thus prevents the patient from receiving important information. One possible solution presented by the industry is to raise more awareness of the exchange of EM between the HCP and the patient through external associations such as the AkdÄ and the AMK. [1, pp. chapter 9, section 4.2]

The requirement to implement EM remains a “one-way obligation” for the pharmaceutical industry. A company is subject to legal requirements, but these are not binding for the HCP or patient [18, p. XVI.C.3]. The only exception as of today, are thalidomide-, lenalidomide- and pomalidomide-containing medicinal products, for which the HCP needs to sign a consent to confirm that the safety instructions have been followed and that the patient has received associated information. Since this process is working quite well in practice, industry suggests discussing a similar process for EM and therefore proposes to take this discussion on the authority level. [1, pp. chapter 9, section 4.2]

As mentioned briefly above, the physical distribution of EM by mail is especially expensive due to the high printing and distribution costs. Additionally, the challenge with this distribution method is its focus on HCPs rather than patients. Thus, again, the patient could be side-lined. A general approach that was highlighted by the industry is the digitalisation of EM, which ensures a quick and efficient access to the most current version of the material. External sources can also be used to publish the EM, such as the “Rote Liste”. The MAH can for instance create a short URL (Uniform Resource Locator) or QR code (Quick Response code which can be included in the product information texts, redirecting to a website where the material can be downloaded. Digitalisation often has a pessimistic connotation but according to some feedback data both patients and HCPs have reacted positively to such methods, as they are able to access the material quickly and easily at any given time. [1, pp. chapter 9, section 4.3]

The EM is currently also published on the NCA websites, i.e. BfArM (Federal Institute for Drugs and Medical Devices; German: Bundesinstitut für Arzneimittel und Medizinprodukte) and PEI (Federal Institute for Vaccines and Biomedical Drugs; German: Paul Ehrlich Institute) in Germany. This means that two separate registers are

available which is confusing for the target audience because they do not understand the separation of medicinal products between these two authorities. The industry is clearly in favour of linking the two registers. [1, pp. chapter 9, section 4.3]
The MAH is obliged to save the current version of the EM on his website in an easy-to-find place without password protection. In addition, the product information texts should be stored near to the EM as both types of documents should be read in conjunction. In order to simplify this task, to keep the company's website well-arranged and to make the access as easy as possible for the reader, the industry proposes to create a separate website with its own link within the borders of the company's website. All authority approved information can be stored there. [1, pp. chapter 9, section 4.3]

Measuring the effectiveness of risk minimisation measures is a major challenge for the industry as complex tools and instruments are required to evaluate them [1, pp. chapter 9, section 4.2]. Meaningful indicators need to be developed to measure actual effectiveness, e.g. whether the measure reached the target group, whether the message was understood by the audience or whether a reduced frequency of side effects is achieved [18, p. XVI.B.4.2.].

The above discussed challenges and possible solutions/ demands from the industry are summarised in Table 5.

Table 5: Summary of challenges related to RMPs & aRMM identified by the industry and positions/demands

identified challenges	position/demands
RMP creation	
Complex process which requires proper project management, thus a high resource investment	
National RMP requirements differ	Agency to provide harmonised RMP template which can be used in every country
RMPs across MAHs are not harmonised	Create further simplification by speeding up project HaRP
Decision of what is an important risk is still challenging	

identified challenges	position/demands
DHPC creation	
Complex process to create DHPC which requires proper project management → high resource investment	
If more MAHs are involved, complexity rises	Coordination support by industry associations
DHPC distribution	
Most commonly by postal mail → expensive & time consuming compared to digital solutions	Share costs between all MAHs and industry associations to support as coordinating role
Postal mail takes a few days → not available immediately	Introduce digital solutions
All MAHs must work together which increases the complexity	Coordination support by industry associations
EM creation	
Complex process to create EM which requires proper project management, thus a high resource investment	
No sale of product unless EM is approved and delivered to the target audience → risk of loss in sales	Start preparation as early as possible and minimize internal tiemlines as much as possible
Creation of EM for generic products in alignment with the originator product is challenging due to trademark issues	Agencies to provide harmonised education material templates that can be used for generic products
The need of EM is decided on national level and can differ in countries	More alignment on NCA level between the countries & transparent decision-making for the need of EM
Constant maintenance of EM	
A survey concluded that the reader sometimes misses the clear focus on the safety concern	Agencies to fine-tune the content & layout together with MAH
Data showed that content is sometimes not user friendly	Generate receipient-specific material
Lack of awareness of the existence of EM by recipients	MAH and other associations (NCA, AkdÄ, AMK,…) to promote blue hand logo and its intention

identified challenges	position/demands
Handover of EM from HCP to patient is sketchy	MAH and other associations (NCA, AkdÄ, AMK,…) to create more awareness for sharing
Obligation to implement EM is limited to the MAH and not to HCPs	Authority to create a tool to make HCPs responsible
EM NCA review	
Review process takes significant time	Keep lose and pragmatic contact with NCA
EM distribution/publication	
Postal mail is expensive & time consuming compared to digital solutions	Introduce digital solutions
Postal mail focuses only on HCPs and not on patients	Introduce digital solutions to reach the complete taregt audience
Confusion by reader regarding NCA website where EM is published → separate registers from BfArM and PEI	Link registers
Publication of EM on MAH website must be easy to find without password protection	Creation of separate website with its own URL within the boudaries of the MAH website
DHPC/EM effectiveness evaluation	
Measuring the effectiveness of risk minimisation measures is a major challenge	

3.6 Maintenance of licenses

The legal requirements and the respective PV activities the industry is confronted with related to the maintenance of licenses have been summarised and put in relation to other critical PV processes and tools in chapter 2.6. The aim of this chapter is to highlight identified challenges according to the industry's perspective and to outline possible solutions or proposals/demands as defined by them in order to simplify the processes and tasks in the complex PV network.

The workload related to the maintenance of licenses binds a lot of resources in the RA department, which is responsible for the preparation and submission of the variation, but also in other departments, such as Pharmacovigilance, Medical Affairs and Marketing, which are involved in providing data and documents for the variation submission package. Adequate project management helps to handle this process, but this requires significant resources.

The variation planning is an essential and time-consuming phase. Each change must be addressed within an associated change control, where a regulatory impact assessment is required. This process is very time-consuming since the change and its consequences must be understood in detail in order to be able to choose the correct variation category. The associated tasks, including due dates, are specified in the change control and the necessary documentation for the submission package is documented. It is of utmost importance to communicate this to all stakeholders in order to ensure adequate preparation time and thus a timely submission.
In terms of classifying the variation, industry raised concerns because of their critical view of some of the classification rules. One example is the deletion of an indication that is classified as type IB variation, which is seen to be too stringent [1, pp. chapter 10, section 2]. The deletion of an indication cannot pose a risk to the patient or raise safety concerns, therefore it should be downgraded to a type IA variation [1, pp. chapter 10, section 2].
Another example given by the industry, was that all safety variations related to new MAH data are classified as type II variation, which they again see as too stringent. The justification for this is that the addition of safety information to the product information texts, e.g. warning statements or additional instructions for handling, always lead to greater safety for the patient. Therefore, the industry demands a downgrade of such changes to a type IA variation, because this would ensure a faster implementation on the market and thus a faster transmission of the information to the HCP or patient. The

MAH is legally responsible for missing risk information in the product information texts, therefore a delay in transmission is seen critically by industry. [1, pp. chapter 10, section 5.2] Generally, the higher the variation category, the more costs arise for the MAH, the longer the review process, thus the longer it takes to implement the change. This is also criticised by industry as it delays the immediate update of product information texts [1, pp. chapter 10, section 5.2].
In addition, most MAHs handle different variations simultaneously every day. Multiplied by the number of licenses, this results in a significant workload only from managing and tracking these variations. Furthermore, if several variations are ongoing in parallel, which all affect the product information texts, multiple versions of the texts are being created containing different changes. Since approval and implementation dates can differ from variation to variation, maintaining an overview of alternate versions of the texts as well as when which change must be implemented. This creates an overwhelming workload for the MAH and may lead to mistakes by implementing the wrong changes at the wrong time.

The RA department leads the preparation of the submission package, coordinating all involved departments. When product information texts are updated, most companies have an internal review process that involves other departments, such as Medical Affairs and Marketing. This internal review often takes a lot of time and resources, especially when multiple cycles are required. However, it is necessary to review the changes from the perspective of each department. Apart from that, the submission package must be prepared by RA employees, including cover letter and other administrative documents.

Once the submission package has been submitted to the NCA, the review process starts. In practice, sometimes different approaches are seen by the NCA assessors. A lot of text changes are very subjective in terms of wording or format details and differ from country to country, from assessor to assessor. This leads to unnecessary increase in complexity.

After variation approval, the change must be implemented. In terms of changes to the product information texts, artwork must be updated. While this may seem simple, it can represent a major challenge for companies. Updating the artwork means that the artwork files need to be adjusted, internally reviewed by several departments, approved before they can be printed and shipped to be used for the next production run. This means a significant lead time before market implementation is completed. In larger companies this process can take up to 6 months. The regulatory timelines for the national

implementation differ in each country. However, the implementation date is a critical parameter as it sets the legal timeframe, from which time onward the new package material must be use for production. Releasing product with outdated artwork after the implementation due date makes the product “incompliant”, as the artwork does not comply with the marketing authorisation. In the worst case this can lead to a product recall. The different implementation dates in each country make it particularly challenging for the MAH to manage and track all these timelines, which again ties up significant resources within the company and considering that a company may be marketing numerous products in multiple countries simultaneously, multiple changes of artwork may be necessary.

The pharmaceutical industry highlighted two general aspects and challenges associated with changes to the product information texts: First, product information texts for the same medicinal product from different MAHs are not always harmonised, which can confuse HCPs and patients. Generic companies also face a major challenge, as they are required to align the texts with the originator texts, which is challenging if divergent information is available. [1, pp. chapter 10, section 5.1]
Secondly, the ever-growing standardised phrases in the product information texts make it difficult for the reader to identify critical information. HCPs are often under time pressure and are unable to read the entire text which can lead to an increase in medication errors or off-label use. Patients also react negatively when overloaded with information. [1, pp. chapter 10, section 5.4]

The above discussed challenges and possible solutions/ demands from the industry are summarised in Table 6.

Table 6: Summary of challenges related to maintenance identified by the industry and positions/demands

identified challenges	position/demands
Variation planning	
Deletion of indication is a type IB variation	Should be downgraded to type IA
All safety variations related to new MAH data are classified as type II variation	Should be downgraded
Too many text variations in parallel can lead to the implementation of the wrong changes	Try to combine as much text changes as possible in one variation; excellent tracking tools need to be in place
Variation preparation	
Internal review of submission documents is very time consuming	Try to avoid multiple review cycles by defining clear rules for everyone
Variation review & approval	
Different review approaches by assessors rise complexity for MAH	
Change implementation	
Long lead times for update of artwork	Try to avoid multiple review cycles of the artwork and squeeze internal lead times as much as possible
National differences in implementation dates	
General aspects	
PI texts from different MAH are not always harmonised → challenge for HCP/patients and for generic companies	Agencies should aim for more harmonised product information texts
Ever-growing standardised phrases in the product information texts make it difficult for the reader to identify the critical information	Agencies to focus on the most important phrases and keep standardised phrases to a minimum

3.7 Pharmacovigilance Audits

The legal requirements and the respective PV activities the industry is confronted with related to referrals have been summarised and put in relation to other critical PV processes and tools in chapter 2.7. The aim of this chapter is to highlight identified challenges according to the industry's perspective and to outline possible solutions or proposals/demands as defined by them in order to simplify the processes and tasks in the complex PV network.

The worldwide distribution of a medicinal product requires PV presence in every country where it is marketed. Usually affiliates located in key markets are also responsible for local PV activities, in other markets however the MAH is forced to outsource this responsibility to external providers/partners. This leads to a complex structure of PV processes and requires intensive management of PV partners including time- and resource binding audits. Due to a long list of PV partners and contractors (big companies have around 50-100 partners/contractors) many companies are not able to fulfil the legal requirements for audits, which makes them "incompliant". The fact that an audit must be carried out at a minimum every 5 years illustrates the difficulties this entails.
Furthermore, the PV department often is not involved in the selection of partners/contractors but is still required to cooperate during the course of the partnership. It is advisable to involve the PV department in the selection process. [1, pp. chapter 12, section 1]
Industry has identified many challenges related to the performance of audits, which are highlighted in the following paragraphs:
The audit planning and preparation phase is imperative as it determines the level of detail for the later execution of the audit.

- The scope of an audit is much stricter today than in the past, where findings were based solely on patient safety. Nowadays, regulatory issues also trigger a finding, resulting in extensive follow-up measures. This is criticised by the industry as patient safety should remain the focus of all audit activities. [1, pp. chapter 12, section 4.1]
- Audit preparation is very time consuming, especially if the audit takes place in another country. However, it is one of the most important activities as it can reduce the time needed for the actual audit on-site. [1, pp. chapter 12, section 4.2]
- Communication with the partners/contractors about the upcoming audit is key. They are often very insecure about the upcoming audit, thus there might be limited commitment, e.g. to provide the necessary information. This can jeopardise the

success of the audit. It is important to make clear that an audit is not an inspection and that everyone should be open-minded and constructive. In addition, close contact with the partner/contractor generally recommended in order to constantly exchange information. This again ties up a lot of resources within the company but is crucial. [1, pp. chapter 12, section 4.2]

During audit execution the industry highlighted the following challenges:

- An on-site audit takes approximately 5 working days, which quickly leads to a cost explosion. From a resource perspective, one person must be available for 5 working days, having no time for any other business. In addition, an on-site audit is always linked to travel expenses. A reduction of this burden could be achieved by promoting remote-audits and by using synergies such as joint-audits. However, agencies would need to officially consent to the possibility of remote audits for this to be an option. [1, pp. chapter 12, section 4.3]
- Audits in other countries are challenging due to time and language differences as well as different cultural and religious aspects. It is essential to build up trust, which requires time and contact. [1, pp. chapter 12, section 4.3]
- Local requirements may deviate from EU legislation, which sometimes makes it difficult to reach agreement between all stakeholders in terms of defining and agreeing on processes. [1, pp. chapter 12, section 4.3]
- As mentioned above, one major problem from industry perspective is that remote-audits are hardly supported by the NCAs. A demand by the industry is that this audit type is fully accepted by the NCAs. In time of globalisation and digitalisation, this is a logical adaption of the conservative approach. There is particularly little risk of performing remote audits when checking the own affiliates, since they belong to the company and processes are well-established and very visible to everyone. [1, pp. chapter 12, section 5]
- From a contractor/partner's point of view, "audit tourism" is a major challenge. One contractor/partner may be responsible for various MAHs and if every MAH performs the audits separately, the number of audits would exceed the usual level and would quickly lead to a time and resource burden for the contractor/partner. The use of joint audits would help to reduce the burden for everyone involved, especially for the contractor/partner. However, there are a few challenges reported from the industry regarding joint audits. First, they are only suitable for standardised processes and therefore only discuss common regulatory requirements and not individual processes and tasks. As a result, the MAH cannot only rely on remote audits but is also required to carry out a face to face on-site

audit from time to time. Second, the coordination between the MAHs within the consortium is complex and leads to a more difficult and time-consuming audit preparation. As this topic is still quite new, there is still unclarity regarding the contract design between the auditor and the consortium, which is a critical part as the MAHs remain legally responsible. Furthermore, it is important that the data protection and confidentiality of the data is ensured and reflected in great detail in the contract. The disclosure of information to the auditor may be sometimes difficult. Therefore, it remains to be seen how these types of audits will prove themselves in practice. [1, pp. chapter 12, section 6]

As soon as the audit is over, the post-audit tasks begin:

- CAPAs and follow up actions are very time consuming. All findings must be treated immediately and must be eliminated as soon as possible. They remain in the PSMF until they are completed and removed from there. CAPAs must be tracked and completion must be documented. Therefore, the time after an audit still requires appropriate resources which must be available within the company. [1, pp. chapter 12, section 4.4]
- The verification of effectiveness of CAPAs must be performed by the QPPV (Qualified Person Pharmacovigilance), which is a challenging task. [1, pp. chapter 12, section 4.4]

The above discussed challenge and possible solutions/ demands from the industry are summarised in Table 7.

Table 7: Summary of challenges related to audits identified by the industry and positions/demands

identified challenges	position/demands
MAH need to often outsource the PV activities due to worldwide distribution of product	Perform more remote audits & keep duration of audit to a minimum by close contact and precise audit preparation
High number of audits for large companies	
Audits at least every 5 years	
PV department often not involved in selection of PV partners/contractors	Involve appropriate functions in the selection process

identified challenges	position/demands
Audit planning & preparation	
Much stricter scope of audit nowadays → patient safety and regulatory requirements	Patient safety should remain to be in focus of all audit activities
Audit preparation very time consuming, but critical step	
Communication with partner about upcoming audit is key, but time consuming → often limited commitment and fear by partner	Promote open-minded and constructive communication and take away fear
Audit execution	
On-site audit is approx. 5 working days	Perform more remote audits & keep duration of audit to a minimum by close contact and precise audit preparation
Audits abroad are difficult due to differences in culture, language and religious aspects	
Audits abroad: local PV requirements often deviate from EU legislation	
Remote audits are hardly supported by NCAs	Audit type must be fully accepted by NCAs
Joint Audits: process still unclear and complex to handle; issue that not all aspects can be addressed	
Post-audit phase	
CAPAs and follow-up actions are very time consuming	
Verification of effectiveness of CAPAs is challenging	

4 Conclusion and outlook

When looking and the PV processes and activities discussed in Chapter 2, it becomes clear how extensive the PV legislation in Europe is. Regulatory requirements have grown immensely in recent years to further improve the safety of medicinal products for European patients. But while this necessary legislative focus on patient safety is an understandable priority, the larger regulatory landscape has led to many individual processes becoming unclear or bloated and not sufficiently streamlined. Frequently this results in redundant workflow or processes that do not add value to the user of the medicinal product and leads to significant resources being wasted in companies which otherwise could be used on the critical issues of a medicinal product - the MAH should not be hampered by regulatory workload with does not stand in any appropriate relation with the output in terms of patient safety. Sometimes laws even contain contradictory regulation, making it challenging industry to adhere to all requirements, even with the best intentions to do so and an ample investment of resources. Thus, to act in the best interest of the patient, it seems necessary to simplify and streamline processes and to limit redundancies to a minimum, so that pharmaceutical companies can focus on critical tasks and product improvement.

For this reason, it is necessary to communicate these challenges and to present appropriate solutions form the industry perspective, which was accomplished perfectly with the publication of the paper series. Industry associations and authorities seem keen to develop a dialogue with industry in order to eliminate issues such as regulatory vagueness and uncertainties. The voice of the industry should be taken seriously, and steps should be taken to address the issues discussed in this thesis. As of now, it remains to be seen whether simplification measures will be implemented and if and how the workload for the companies will be reduced.

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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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