The pharmacovigilance of veterinary medicinal products under Regulation (EU) 2019/6 : introduction of the Pharmacovigilance System Master File

Masterarbeit

zur Erlangung des Titels

“Master of Drug Regulatory Affairs, M.D.R.A.”

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Dr. (DMV) Magali Quetin

geboren in

St Martin d'Hères (Frankreich)

Düsseldorf / 2022

Betreuerin und Erstgutachterin: Prof. Dr. Barbara Sickmüller

Zweitgutachter: Prof. Dr. Burkhard Sträter

Table of Content

ABBREVIATIONS....3
LIST OF TABLES....4
DEFINITIONS....5
INTRODUCTION....1
MATERIALS AND METHODS....3
1 FROM THE DETAILED DESCRIPTION PHARMACOVIGILANCE SYSTEM TO THE PHARMACOVIGILANCE SYSTEM MASTER FILE....5
1.1 LEGAL SITUATION....5
1.2 SIMILARITIES....5
1.2.1 Similarities in purposes....5
1.2.2 Similarities in content....7
1.3 A NEW CONCEPT....8
1.3.1 PSMF and Marketing Authorization dossier....8
1.3.2 Organization of the document....10
1.4 THE NEW ITEMS....11
1.4.1 Section A on administrative information related to the PSMF....11
1.4.2 Annex I: Logbook....12
1.4.3 Annex III.1: List of products....13
1.4.4 Annex III.3: List of local PV responsible....13
1.4.5 Annex IV.2: List of scheduled and completed audits including outstanding critical and major findings....14
1.4.6 Annex IV.3: List of Key Performance Indicators....15
1.4.7 Annex IV.5: Methodology to calculate the dose factor....15
1.4.8 List of risk management measures and outcome....16
1.5 A NEW FOCUS....16
1.5.1 The Quality Management System....16
1.5.2 The Document Management Systems....20
1.5.3 The Risk Management System....21
2 THE PSMF AS INSTRUMENT FOR THE OVERSIGHT OF THE PHARMACOVIGILANCE SYSTEM AND ITS ACTIVITIES....23
2.1 FUNCTIONALITIES OF THE NEW DOCUMENT....23
2.1.1 The PSMF in the scope of regulatory controls and inspection....23
2.1.2 PSMF location and Supervisory Authority....24
2.1.3 PSMF as tool to define the inspection program using a risk-based approach. .26

2.1.4 Information contained in the PSMF and inspection conduction....28
2.2 THE PSMF AS INSTRUMENT FOR THE OVERSIGHT OF THE PHARMACOVIGILANCE SYSTEM AND ITS ACTIVITIES BY THE QPPV 29
2.2.1 One place to find current information on the PV system and its activities....30
2.2.2 Limitations....31
2.2.3 Scope of the data....35
3 IMPLEMENTATION OF THE PSMF....36
3.1 SURVEY....36
3.1.1 Descriptive presentation of the results of the survey....36
3.1.2 Discussion....38
3.2 CREATION OF THE FIRST VERSION: CHALLENGES AND STRATEGIES..38
3.2.1 Novelty....38
3.2.2 Availability of the secondary legislation....39
3.2.3 Availability of the data within the company....40
3.3 MAINTENANCE PROCESS WITHIN THE COMPANY....41
3.3.1 Accuracy and completeness of the data....41
3.3.2 Updates....41
3.3.3 Filing and archiving....44
3.3.4 Publication of the PSMF for submission....45
3.4 INTRODUCTION WITHIN THE MARKETING AUTHORIZATION DOSSIER 47
3.4.1 Creation of the PSMF summary....47
3.4.2 PSMF summary and the Union Product Database....48
3.4.3 Variation Not Requiring an Assessment (VNRA)....48
4 DISCUSSION AND CONCLUSION....50
SUMMARY....54
LITERATURE REFERENCES....55
ANNEXES....58
ANNEX I: COMPARISON OF STRUCTURE AND CONTENT OF THE DDPS AND THE PSMF....59
ANNEX II : OVERSIGHT OF THE QPPV....71
ANNEX III: SURVEY – FORMS....78
ANNEX IV: SURVEY – RESULTS....79

ABBREVIATIONS

Abbreviation	Description
CAPA	Corrective and Preventive Action
CVMP	Committee of Veterinary Medicinal Product
DDPS	Detailed Description Pharmacovigilance System
DMS	Document Management System
EMA	European Medicine Agency
EU	European Union
IR	Implementing Regulation
KPI	Key Performance Indicator
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MIT	Medically Important Terms
PDF	Portable Document Format
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QM	Quality Management
QMS	Quality Management System
QPPV	Qualified Person for Pharmacovigilance
ROR	Reporting Odds Ratio
UPD	Union Product Database
VGVP	Guideline on veterinary good pharmacovigilance practices
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VNRA	Variation Not Requiring an Assessment

LIST OF TABLES

Table 1: content and structure of the DDPS as presented in Part I.2.2.3 VOL 9B

Table 2: content and structure of the PSMF as presented in VGVP module on PSMF

Table 3: parts and items of the PSMF linked to the quality management cycle

Table 4: signal management under VOL 9B and REG 2019/6

Table 5: pharmacovigilance system related factors of risk and the emplacement of the potential information in the PSMF

Table 6: PSMF annexes grouped by items that change rather frequently or occasionally – a proposal

DEFINITIONS

Term	Definition / Explanation
Pharmacovigilance System Master File	According to Art. 4 para. 31 REG 2019/6, *"a detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised veterinary medicinal products."* [1]
Performance indicator	According to Art. 1 IR 2021/1281, "*an item of information collected at regular intervals to monitor the performance of a system* ."[2]
Quality management system	According to Art.1 IR 2021/1281, "*a formalised system that provides for comprehensive processes, procedures, and responsibilities for achieving quality policies and objectives to coordinate and direct an organisation's activities and improve its effectiveness and efficiency in this regard on a continuous basis.*" [2]
Qualified Person for Pharmacovigilance	According to Art. 77 para. 8 REG 2019/6, "t*he marketing authorisation holder shall designate one or more qualified persons responsible for pharmacovigilance to carry out the tasks provided for in Article 78. Those qualified persons shall reside and operate in the Union and shall be appropriately qualified and be permanently at the disposal of the marketing authorisation holder. Only one such qualified person shall be designated for each pharmacovigilance system master file.* [1]
Signal management process	According to Art. 4 para. 41 REG 2019/6, "*a process for performing active surveillance of pharmacovigilance data for veterinary medicinal products in order to assess the pharmacovigilance data and determine whether there is any change to the benefit-risk balance of those veterinary medicinal products, with a view to detecting risks to animal or public health or protection of the environment.*" [1]
Suspected adverse event (in the scope of the PV system)	According to Art. 73 para. 1 REG 2019/6, "*(a) any unfavourable and unintended reaction in any*

Term	Definition / Explanation
	animal to a veterinary medicinal product; *(b) any observation of a lack of efficacy of a veterinary medicinal product following its administration to an animal, whether or not in accordance with the summary of product characteristics;* *(c) any environmental incidents observed following the administration of a veterinary medicinal product to an animal;* *(d) any noxious reaction in humans exposed to a veterinary medicinal product;* *(e) any finding of a pharmacologically active substance or marker residue in a product of animal origin exceeding the maximum levels of residues established in accordance with Regulation (EC) No 470/2009 after the set withdrawal period has been respected;* *(f) any suspected transmission of an infectious agent via a veterinary medicinal product;* *(g) any unfavourable and unintended reaction in an animal to a medicinal product for human use.*" [1]
Union product database	According to Art. 55 para. 1 REG 2019/6, "*the Agency shall establish and, in collaboration with the Member States, maintain, a Union database on veterinary medicinal products ('product database')*." [1]
Union pharmacovigilance database	According to Art. 73, para.1 REG 2019/6, "*the Member States, the Commission, the Agency and marketing authorisation holders shall collaborate in setting up and maintaining a Union pharmacovigilance system to carry out pharmacovigilance tasks with respect to the safety and efficacy of authorised veterinary medicinal products in order to ensure continuous assessment of the benefit-risk balance.*" [1]

INTRODUCTION

The veterinary pharmaceutical industry faced important changes in the legislation framework for veterinary medicinal products in the European Union (EU) with the implementation of the Regulation (EU) 2019/6 on 28 January 2022. On its web-page, the European Medicine Agency (EMA) states that "*the new Veterinary Medicines Regulation (Regulation (EU) 2019/6) updated the existing rules on the authorization and use of veterinary medicines in the European Union (EU) when it became applicable on 28 January 2022.*" [3] Among others, the Regulation (EU) 2019/6 includes a complete revision of the post-marketing pharmacovigilance requirements, with the aim to "*simplify the regulatory environment and reduce administrative burden for pharmaceutical companies developing veterinary medicines, for example through streamlined pharmacovigilance rules.*" [3] The changes are extensive, and the way the profile of authorized products is monitored has been fully modified, with far-reaching consequences for the processes within companies. A single master thesis would not be able to present all the aspects of the new regulation and therefore this master thesis will focus on the Pharmacovigilance System Master File (PSMF) only.

The Regulation (EU) 2019/6 requires the creation and maintenance of a PSMF for the description of the pharmacovigilance (PV) system of the company [1]. In the previous veterinary legislation - Volume 9B of The Rules Governing Medicinal Products in the European Union - a Detailed Description of the Pharmacovigilance System (DDPS) was required [4]. A comparison of the two documents will support the understanding of the novelty introduced with the PSMF: while the purpose is the same, i.e. to describe the PV system, a new concept for the document structure and new items included into the PSMF are shifting the focus of the description.

Based on the understanding of structure and focus of the PSMF, this master thesis will show in a second part the use of this document, far beyond a simple description of the

PSMF. The Regulation (EU) 2019/6 has already placed the PSMF in the middle of the PV inspection: Member States are expected to conduct regular check of the PSMF and its adequacy with the implemented PV system [1]. This master thesis will show that the PSMF is also a good support for the Qualified Person for Pharmacovigilance (QPPV) to oversee the PV system and its activities.

The last part of this master thesis will present the rules to consider when it comes to the implementation of the PSMF in a veterinary company. Especially the processes to create and maintain the PSMF needs to be carefully evaluated for their impact on the workload in PV teams. This master thesis will also discuss if the promise for a lower administrative burden could have been achieved with the implementation of the PSMF.

MATERIALS AND METHODS

To generate this master thesis, I used the following approaches:

1 Review of existing and applicable regulatory documents:

1.1 In-deep analysis of the available legislation, including secondary legislation and guidance published until now in direct relation with the PSMF:

- The Regulation (EU) 2019/6 (in the following, REG 2019/6) [1]
- The Implementing Regulation (EU) 2021/1281 (in the following, IR 2021/1281) [2]
- The Guideline on veterinary good pharmacovigilance practices (VGVP) - Module: Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files (in the following: VGVP on PSMF) [5]
- The Guideline on Veterinary Good Pharmacovigilance Practices (VGVP) - Module: Controls and pharmacovigilance Inspections (in the following VGVP on inspections) [6]
- The Guideline on Veterinary Good Pharmacovigilance Practices (VGVP) - Module: Signal Management (in the following VGVP on signal management) [7].

1.2 A detailed comparison of the former legislation applicable to the PV activities for veterinary medicinal product, i.e. Volume 9B of The Rules Governing Medicinal Products in the European Union , with the new legislation, including secondary legislation and guidances (in the following VOL 9B) [4]

2. Information and presentations of the European Medicinal Agency (EMA) and the authorities to the veterinary pharmaceutical industry during webinars and shared on their respective webpages: it provides insights in the intentions and expectations of the authorities.

3. A survey on the implementation of the requirement for a PSMF in veterinary pharmaceutical companies, distributed via the pharmacovigilance working group of Animal Health for Europe and the Bundesverand der Pharmazeutischen Industrie: the results are presented and discussed in the third part of the master thesis

4. My own experience with the implementation of the Regulation 2019/6 and with the creation of a PSMF for a large veterinary pharmaceutical company.

1 FROM THE DETAILED DESCRIPTION PHARMACOVIGILANCE SYSTEM TO THE PHARMACOVIGILANCE SYSTEM MASTER FILE

The **Detailed Description Pharmacovigilance System (DDPS)** can be seen as the 'ancestor' of the **Pharmacovigilance System Master File (PSMF)**. This section will present the similarities and important differences between the two documents.

1.1 LEGAL SITUATION

The implementation of the REG 2019/6 repealed the Directive 2001/82/EC [1: Art. 149]. De facto the secondary legislation and guidance under the governance of the Directive 2001/82/EC become obsolete. For example, the VOL 9B [4].

A range of secondary legislation and guidance has been created. Particularly relevant for the PSMF are:

- the IR 2021/1281 [2]
- the VGVP on PSMF [5]
- the VGVP on inspections [6].

1.2 SIMILARITIES

1.2.1 Similarities in purposes

Whereas the legislation framework has been renewed, principles of pharmacovigilance have remained. The obligation is made to Marketing Authorization Holders (MAHs) to have in place a PV system:

Part I.2.3.3 VOL 9B	Art 77 para. 1 REG 2019/6
"All MAHs are required to have an appropriate system of pharmacovigilance in place." [4]	*"Marketing authorisation holders shall establish and maintain a system for collecting, collating and evaluating information on the suspected adverse events concerning their authorised veterinary medicinal products, enabling them to fulfill their pharmacovigilance responsibilities ('pharmacovigilance system')*." [1]

From this obligation ensues the necessity to define a document dedicated to the organized and standardized description of the PV system in the company:

Part I.2.3.3 VOL 9B	Art. 22 para. 1 IR 2021/1281
"The Detailed Description of the Pharmacovigilance System should include the following elements, as applicable, and be set out in a structured manner consistent with this list. Additional important elements pertinent to a specific situation should be added." [4]	*"The pharmacovigilance system master file shall consist of a main part describing the pharmacovigilance system, together with annexes containing detailed information."* [2]

Both DDPS and PSMF are reflecting the items being part of a PV system and that MAHs should consider to have in place for their own system. In that sense, both DDPS and PSMF

are the expression of the current understanding amongst authorities in Europe on what PV stands for and how PV activities should be performed.

PV systems are considered subject to continuous changes, because of the introduction of improvements in the processes and tools used, or because of contingency within the company (e.g. restructuring in the scope of a merger). Therefore, the authorities expect regular updates of either DDPS or PSMF in order to capture the changes in the PV system:

Part I.2.3 VOL 9B	Art. 24 para. 1 IR 2021/1281
*"Updates to the information provided in the DDPS should be made in accordance with current legislatio*n." [4]	*"Marketing authorisation holders shall keep the pharmacovigilance system master file up to date and revise it, where necessary, to take account of experience gained, and of technical and scientific progress*." [2]

However, the ways how the changes are captured, tracked and notified to authorities are different (see sections 1.3.1 on logbook and 3.3.2 on variations not requiring assessment).

1.2.2 Similarities in content

Table 1 and table 2 present respectively the content and structure of the DDPS and the PSMF.

Table 1: content and structure of the DDPS as presented in Part I.2.2.3 VOL 9B [4]

a) QPPV
b) Organization
c) Procedures in place, which are documented in writing
d) Databases

e) Contractual arrangements with other persons or organizations involved in the fulfillment of pharmacovigilance obligations
f) Training
g) Documentation
h) Quality Management System
i) Supporting documentation

Table 2: content and structure of the PSMF as presented in VGVP module on PSMF [5]

Section	Main part	Annexes
Information of the PSMF	Section A	Annex I
QPPV, assisting veterinary surgeon, and back up procedure	Section B	Annex II
Marketing Authorization holder information	Section C	Annex III
Document management system (including record management system for adverse events recording)	Section D	No corresponding annex
Quality management system (QMS) for pharmacovigilance activities	Section E	Annex IV
Contractual arrangements between marketing authorization holders and third parties concerning pharmacovigilance activities	Section F	Annex V

It is noticeable that the same overarching topics can be found in both documents. Therefore, a comparison of the two documents can easily establish the wide overlap, as shown in Annex I: Comparison of structure and content of the DDPS and the PSMF. Nevertheless, there are a few fundamental differences that will be explained in the following.

1.3 A NEW CONCEPT

1.3.1 PSMF and Marketing Authorization dossier

The DDPS was part of the application dossier and submitted to the authorities with each application [8: Art. 12 para. 3 Regulation 2001/81/EU], whereas with the new concept of

PSMF, only a PSMF summary is now included in application dossiers as per Art 8 para. 1(c) REG 2019/6: "*An application for a marketing authorisation shall contain the following: […] (c) a summary of the pharmacovigilance system master file*." [1] For details on the content of the PSMF summary and its introduction to existing Marketing Application dossiers, reference is made to section 3.3.1.

The PSMF itself is kept at the Marketing Authorization Holder (MAH) and will be provided to the authorities upon request only. [2: Art. 24 para. 5 IR 2021/1281]

The REG 2019/6 also states in article 77 paragraph 1: "*[…] For each veterinary medicinal product, the marketing authorisation holder shall not have more than one pharmacovigilance system master file.*" [1] The VGVP on PMSF further specifies that "*while each PSMF and QPPV will be linked to one or more veterinary medicinal products, each product authorised under Regulation (EU) 2019/6 should be linked to a single PSMF and the respective designated QPPV.*" [5: section 2.3.1]

In practice, the following 'equation' prevails:

ONE PV system

is described in ONE PSMF

that is led by ONE QPPV

but covers SEVERAL marketing authorizations.

While this was already true with the DPPS, it becomes more visible with the PSMF (see sections 1.4.1 and 1.4.2). The link between PSMF and Marketing Authorizations (MAs) is the Union Pharmacovigilance Database: a number is assigned to the PSMF, which shall be registered in the Union Pharmacovigilance Database as per Art. 74 para. 1 REG 29019/6.

[1]. In practice, in each record of the MAs tracked in the Union Product Database (UPD), the number of the PSMF appears: "*the information from the summary of the applicant's pharmacovigilance system master file (QPPV name, contact details and location, PSMF reference number and location) will be stored in the Union product database and communicated to the Union pharmacovigilance database.*" [5: section 2.3.1]

1.3.2 Organization of the document

With the PSMF, the REG 2019/6 introduces a new concept for the organization and presentation of the information related to the PV system, which was successfully implemented in human pharmaceutical companies approximately 10 years ago. Reference is made to Art. 104 para. 3(b) Directive (EU) 2010/84 [9], and to Art. 2 Regulation (EU) 2012/520 [10].

The PSMF consists in a main part divided into several defined sections and a series of annexes. In its 'Scientific Recommendation for Implementing Measures under Article 77(6) of Regulation (EU) 2019/6 on veterinary medicinal products regarding the pharmacovigilance system master file from 29 May 2020' (EMA/CVMP/123178/2019), the expert group from the Committee of Veterinary Medicinal Product (CVMP) underlined that the intention was to have:

"a main part with basic information required to describe the pharmacovigilance system, and annexes containing information that may be subject to frequent change and which is useful for the pharmacovigilance system oversight, audits and inspections." [11]

Therefore, the main part is rather a textual description of items, illustrated with figures when deemed appropriate, where lists, tables and other collation of data are expected in annexes.

Art. 22 IR 2021/1281 presents and details the main part and the annexes to be generated by the MAHs while creating their PSMF [2]. Systematic cross-references to other articles

of the IR 2021/1281 and to the REG 2019/6 are made along with the enumeration of the items, in order to specify the content expected. For example, when Art. 22 para. 3 IR 2021/1281 requires a list of written procedures in annex VI.1, and refers to Art. 4 para. 3, 4, 5 and 6 IR 2021/1281 for details on the processes for which procedures should be available. [2]

From the comparison of the contents between DDSP and PSMF, presented in Annex I: Comparison of structure and content of the DDPS and the PSMF, it is obvious that the structure of the information, even similar, has been strongly revisited by the legislator. Also, the scope of the information requested has been widen and many new items have been introduced.

1.4 THE NEW ITEMS

Several new items have been introduced in the PSMF, that were not presented in the DDPS. A few significant examples will demonstrate in the following how much the PSMF is different from the DDPS. Reference is made to Annex I: Comparison of structure and content of the DDPS and the PSMF for comparison of the organization and items in both documents.

1.4.1 Section A on administrative information related to the PSMF

There is a need to identify the PSMF in assigning a number to the document. It is the responsibility of the QPPV to assign this number, as stated in Art. 78 para. 1(b): "*1. The qualified person responsible for pharmacovigilance as referred to in Article 77(8) shall ensure that the following tasks are carried out: […] (b) allocating reference numbers to the pharmacovigilance system master file and communicating that reference number to the pharmacovigilance database for each product.*" [1]. During a webinar organized by EMA on December 8th 2021, Sophia Mylona explained on behalf of EMA that for the number:

> *"i. any reference can be selected following the format: PSMFXXXXXXX (free text field)*

ii. PSMF reference number should be unique for the MAH & for the group of products it relates to

iii. expectation that combination of PSMF reference – PSMF location – MAH organization will be unique at EU level." [12: slide 25]

It is expected that an upcoming revised version from the EU Implementation Guide (Vet EU IG) on veterinary medicines product data in the Union Product Database, Implementation of the requirements of Regulation (EU) 2019/6 for the Union database on veterinary medicinal products in the European Economic Area, (EMA/444352/2021), will confirm and document this requirement. [13]

The location of the PSMF is also an important item, because it determines the local authorities that will be in charge of the PV inspection. Reference is made to section 2.1.1 for further details.

The importance of number and location of the PSMF results in the need to have this administrative information also included in the document itself: this is done within the section A.

1.4.2 Annex I: Logbook

The PSMF is *per definitionem* a living document, that will be adapted to the modifications and improvements implemented in the PV system. And the information included in annexes are subject to frequent changes.

Art. 22 para. 3(a) IR 2021/1281 foresees the creation of a logbook for tracking the changes and adaptations made to the main part of the PSMF [2]. In VGVP on PSMF, it is specified that "a*ny alteration to the content of the main part of the PSMF made within the last 5 years shall be recorded in a logbook*". [5: section 2.3.3]. I.e. the document contains its own history as a separate annex.

Furthermore, the logbook allows to document any relevant changes into the PV system of the MAH that are not reflected in the PSMF summary and as such not subject to notification to the authorities via variation. This is an important difference to the DDPS: each amendment of the descriptions and information included in the DDPS was subject to the submission of variations and notified to the authorities. In the case of the PSMF, the logbook is therefore an important instrument during inspection. Likewise, it is a source of information for the QPPV supporting the oversight of the PV system. These aspects will be developed in section 2.

1.4.3 Annex III.1: List of products

Companies may use different PV systems in their organization, addressing the needs for PV activities of distinct parts of their portfolio (e.g. pharmaceuticals versus vaccines and biologicals). This may encompass the oversight by different QPPVs, the use of different processes and procedures, the storage of information in different PV databases, etc. Art. 23 para. 3 IR 2021/1281 acknowledges this situation. [2]

The DDPS was embedded in the application dossier for a product and it was obvious that the PV system described in the DDPS was applicable to that particular product. In case of the PSMF, the summary of the PSMF submitted with the application dossier does not contain any reference to the product. Therefore, a list of all veterinary medicinal products covered by the PSMF is required as per Art. 22 para. 3(c) IR 2021/1281. [2]

Companies are allowed to have distinct PV systems for different part of the portfolio, hich are then described in different PSMFs. In this case, annex III.2 is required in order to cross-reference the PSMFs maintained by the same MAH as per Art. 22 para. 3(c) IR 2021/1281. [2]

1.4.4 Annex III.3: List of local PV responsible

Beside the nomination of a QPPV, Art 77 para. 3 REG 2019/6 requires that "*the marketing authorisation holder shall designate a local or regional representative for the purpose of*

receiving reports of suspected adverse events who is able to communicate in the languages of the relevant Member States." [1] Art. 22 para. 3(c) IR 2021/1281 describes the provision of the list of the designated persons, including their name and contact details in the annex III.3 of the PSMF. [2]

The author considers that only company's employees and individuals directly contracted by the company for the purpose of being their local representative should be added to this list. In case the company cooperates with a distributor in one or the other EU country for any of the products covered by the PSMF, a PV agreement signed by both parties should establish the respective responsible partner for each PV activity, amongst others the communication with the national authorities. The name and contact details of the respective PV persons should be exchanged in the PV agreement. Such PV agreement is recorded in annex V.3 of the PSMF.

1.4.5 Annex IV.2: List of scheduled and completed audits including outstanding critical and major findings

Information on pharmacovigilance audits is requested in two places in the PMSF:

- Art. 22 para. 2 (e) IR 2021/1281 states that the "*audits associated with unresolved critical or major findings*" are listed in section E. [2]

- in addition, Art. 22 para. 3(d) IR 2021/1281 establishes the annex IV.2 that lists "*all scheduled and completed audits including outstanding critical and major findings*" in addition[2]

Both lists are slightly redundant, and this redundancy emphasizes the importance for the authorities of managing the quality of the PV activities. Furthermore, and because modifications to the main part of the PSMF are captured in the logbook (see section 1.4.2) when changes to the annexes content are not, any PV audit detecting new critical or major findings becomes immediately visible.

1.4.6 Annex IV.3: List of Key Performance Indicators

The IR 2021/1281 introduces the requirement to define and monitor key performance indicators (KPI) for the PV activities, as per Article 7: "*MAHs shall use relevant performance indicators to continuously monitor the performance of PV activities and the outcome of risk minimization measures.*" [2] The section 2.2.2 of the VGVP on PSMF further specifies the expectations of the authorities: "*The items of information that can be collected at regular intervals to track the performance of the system should be realistic and measurable, such as submission timeliness or quality of reports / reports free of errors.*" [5]

In practice, the MAHs are mainly free to establish the KPIs that seem appropriate and meaningful to their PV system: neither REG 2019/6 nor the secondary legislation make any detailed requirement. However, Art. 22 para. 3(d) IR 2021/1281 requires that the description of the KPIs and a justification for their choice are provided in annex IV.3 of the PSMF. The figures resulting from the KPIs monitoring are kept outside of the PSMF.

1.4.7 Annex IV.5: Methodology to calculate the dose factor

This new requirement is linked to the Union Product Database (UPD) and the provision of sales data for each MAs held in the EU. Reference is made to Art. 55 para. 2(d) REG 2019/6 on the Union Product Database: "*The product database shall contain at least the following information: […] the annual volume of sales […] for each veterinary medicinal product.*" [1] The MAHs are expected to provide annual volume of sales for their products to the UPD, as per Art. 58 para. 12 REG 2019/6. [1]

As per Art. 14 para. 2 IR 2021/1281, the dose factor is a numerical multiplicator that concatenates the assumed distribution of sales and the treatment regimen per target species: it allows to estimate the number of treated animals using the sales data. [2] This estimation in turn allows the calculation of incidences of adverse events and is defined in the VGVP on signal management as a useful tool while evaluating and assessing a safety signal. [7: section 2.5] Furthermore, "*the annual incidence data from suspected adverse*

events for each veterinary medicinal product by animal species and type of suspected adverse event should be made available for access to the general public in the Union pharmacovigilance database." [7: section 3.3]

The concept of dose factor is not new and part I.6.3.1.4 VOL 9B required the dose factor used for the ratio and incidence calculation to be discussed within the Periodic Safety Update Report. [4] Since the REG 2019/6 abolished the generation of PSUR, another place has been defined to capture this important information in Art. 14 para. 3 IR 2021/1281: the annex IV.5 of the PSMF. [2]

1.4.8 Annex IV.6: List of risk management measures and outcome

In accordance with Art. 12 para. 3(k) Regulation 2001/82/EU, the applicant was required to provide in addition to its DDPS a description of the Risk Management System applicable for the product concerned by the application. [8] Part I.3 VOL 9B specified that this Risk Management System should present the measures put in place to address specific safety risks detected for the particular product. [4]

With the extension of the scope of the PSMF to a complete portfolio of products, a more holistic view of the risk management measures in place becomes necessary. Art. 22 para. 3(d) IR 2021/1281 requests to list the risk minimization measure in place and their outcome. [2]

1.5 A NEW FOCUS

1.5.1 The Quality Management System

The IR 2021/1281 dedicates a complete chapter to the Quality Management System: Chapter 2 stresses the importance of systematically applied quality concepts and processes to PV activities. [2]

Art. 4 para. 1 IR 2021/1281 requires the MAH to ensure that their PV activities are conducted within the framework of a Quality Management System (QMS): "*The marketing*

authorisation holder shall establish and implement an adequate and effective quality management system for the performance of its pharmacovigilance activities" which should be "*described in the pharmacovigilance system master file*." [2]

The Section E of the PSMF is dedicated to the description of the QMS. Art. 22 para. 2(e) IR 2021/1281 specifies that it should include:

- Written procedures. Art. 4 para. 3 to 6 IR 2021/1281 provide a detailed list of processes for which such a written procedure should be available. It is to note that a written procedure is now also required for the PSMF and its maintenance.

- A training management system. Art. 6 IR 2021/1281 gives the details on the requirement for training of MAH personnel involved in PV activities.

- A documentation and archiving system (see section 1.5.2).

- Quality Assurance audits, including the list of audits associated with unresolved observations and the respective Corrective and Preventive Actions (CAPA). Art. 8 and 9 IR 2021/1281 define additional requirements related to audits, their conduction and documentation, and the authorities' expectations linked to CAPAs. [2]

These elements were also described in the DDPS, but in separated sections, as shown in the Annex I: Comparison of structure and content of the DDPS and the PSMF. Their collation into one section of the PSMF give them more weight and focus the attention on this aspect of the pharmacovigilance framework.

Furthermore, six lists and documents, grouped into the annex IV, supplement the description of the QMS for PV in the section E of the PSMF (see Annex I: Comparison of structure and content of the DDPS and the PSMF for details). This is a new approach. In the past,

MAHs were rather requested to provide this information ahead of or during an inspection. Having them systematically collected and organized in one document is an advantage when preparing an inspection and to ensure oversight by the QPPV, as it will be demonstrated in section 2.

The IR 2021/1281 further specifies the requirements for a QMS adapted to the PV activities:

- Art. 4 para. 7 points out the importance of "*clearly define the roles and responsibilities of those persons involved in pharmacovigilance activities and in documentation.*" [2] . I.e. roles should be defined within the PV system and the written procedures should mention for each process step which role will be responsible to perform this step.

- Art. 4 para. 8 outlines the standard cycle of quality management, which should be applied to the QMS for PV activities:

    - Planning of structures and processes

    - Adherence to processes set-up

    - Control and monitoring, if structures and processes are effectively in place and followed

    - Improvements to correct structures and processes, which would require another cycle of planning, adherence, etc. [2]

Historically, MAHs developed their QMS in relation with clinical studies and manufacturing activities, in order to comply with Good Clinical and Good Manufacturing Practices.

With the implementation of VOL 9B, MAHs developed a set of dedicated procedures for PV activities [4: part I.2.3.3.(c)], ensured the training of their personnels [4: part I.2.3.3.(f)] and the documentation thereof [4: part I.2.3.3.(i)], and monitored during internal audits the compliance with the procedures [4: part I.2.3.3.(h)]. The existing quality management structures (e.g. internal auditors) and processes (e.g. management of standard operating procedures, incl. review cycle, training and filing/archiving) were used and applied to the PV activities. The PSMF will ensure the further development and implementation of quality management principles to the PV activities, for example in monitoring KPIs. Table 3 below shows which parts and items of the PSMF are linked to the quality management cycle.

Table 3: parts and items of the PSMF linked to the quality management cycle

Parts and items of the PSMF [2]	QM cycle
Annex IV.1: a list of documents, policies, procedures and processes used for the pharmacovigilance activities	Planning
Annex IV.2: list of all scheduled and completed audits including outstanding critical and major findings Annex IV.3 a list of performance indicators	Control and monitoring
Annex IV.4 the information on training plans and records	Adherence to processes
Section E: description of the corrective and preventive action plan management and change management in place	Improvements

1.5.2 The Document Management Systems

The Document Management System is considered part of the QMS described above, and requirements are set in Art 5 IR 2021/1281 [2]. The section D of the PSMF is dedicated to the description of the Document Management Systems (DMS) used for PV activities as per Art. 22 para. 2(d) IR 2021/1281 [2].

The key DMS is certainly the PV database used to collate, process and notify the AE reports, also called Record Management System: Art 10. IR 2021/1281 mentions that "*the document management system referred to in Article 5 shall include a record management system for receiving, recording, collating and assessing information on adverse events and for recording safety information.*" [2] It was already subject to a separate section of the DDPS as per Part I.2.3.3(d) VOL 9B. [4] It is to note that the authorities offer all stakeholders to use the Union PV Database as their Record Management System. Art. 10 para. 3 IR 2021/1281 states that "*Marketing authorisation holders may use the Union pharmacovigilance database as their electronic record management system for recording adverse events.*" [2] This is unprecedented initiative, and demonstrates the efforts made by EMA and the authorities to establish a single source of safety information for the product authorized in the EU. At the date this master thesis is written, users rather face massive technical issues with the Union pharmacovigilance database and its functionalities.

Further DMS applicable to the PV activities should also be considered: Art.5 IR 2021/1281 refers to "*Pharmacovigilance data and documents relating to individual authorised veterinary medicinal products [that] shall be retained*". [2] The definition is wide and considerations should be given to the repositories for PV procedures, for audit reports, for training documentation, but also for documents related to the risk management activities. The latter are another new focus of the regulation and therefore of the PSMF, as shown in the next section.

1.5.3 The Risk Management System

In the introduction and justifications of the REG 2019/6, the European Parliament and the Council of the European Union declare: "*It is, however, emphasised that the signal management process is the 'gold standard' for that purpose [i.e. the evaluation of the risk-benefit balance] and proper attention should be given to it. That signal management process consists of tasks of signal detection, validation, confirmation, analysis and prioritisation, assessment and recommendation for action*." [2: whereas 63] After entry into

force of REG 2019/6, signal management becomes the central and unique PV activity that analyses aggregate PV data. The previous generation of Periodic Safety Update Report (PSUR) and their analysis of data over a defined reporting period (e.g. 3 years) have been abandoned. The signal management activities are due at least yearly for each product authorized in Europe as per Art. 17 para. 7 IR 2021/1281. [2] This is a significant shift in the mindset how benefit-risk monitoring for authorized products is conducted in the EU. Main aspects are developed in the VGVP on signal management. Table 4 presents a brief comparison of the main differences:

Table 4: signal management under VOL 9B and REG 2019/6

VOL 9B	VGVP on signal management
PSUR generated according to a fixed schedule [4: part I.6.2.2] and signal detection [4: part I.4.11]	Continuous monitoring of the data newly collected "*in order to promptly detect any new safety issues that may impact the benefit-risk balance so that adequate regulatory actions and communication (where necessary) can be taken*" [7: section 2.1] PSUR abondonned
Identification of an increase of the number of event, or their incidence, new identified events, suspicion of a potential impact on human health or environment [4: part I.4.11]	Mandatory use of the Union pharmacovigilance database for signal detection purpose, once a year [2: Art. 17 para. 7] Consideration of a product-event association in the PV database, using statistical methods of disproportionality like the Reporting Odds Ratio (ROR) [7: section 2.3.3]
Prioritization of the events using seriousness, expectedness and causality assessment [4: part I.4.5.10]	Introduction of the concept of Medically Important Terms (MIT) to prioritize certain medical events by species [7: Appendix I]

It is to note that neither the DDPS nor the PSMF dedicate a specific section or sub-section to the risk management system in place, while the management of safety risk of the veterinary medicinal product is the 'raison d'être' of all PV activities.

MAHs usually described the risk management processes within the section of DDPS dedicated to processes and procedures. In the PSMF, information related to the signal management can be found in different places:

- Section D on DMS, in case the MAH uses a dedicated DMS to record, evaluate and follow-up on detected safety signals,
- Section E and corresponding Annex IV.1 on procedural documents used to perform the PV processes linked to the risk management,
- Annex IV.6 on risk minimization measures and their outcome,
- Annex V.2 on tasks of the QPPV that have been outsourced to a 3rd party, in case the risk management or part of it has been outsourced.

For the latter, it will be interesting to gain more understanding on how the PV inspectors interpret what is an outsourced task in relation with the risk management. For example, will this go so far to include the research institute involved in the conduction of a post-marketing safety study as part of a risk minimization measure?

2 THE PSMF AS INSTRUMENT FOR THE OVERSIGHT OF THE PHARMACOVIGILANCE SYSTEM AND ITS ACTIVITIES

2.1 FUNCTIONALITIES OF THE NEW DOCUMENT

2.1.1 The PSMF in the scope of regulatory controls and inspection

Art. 77 para. 2 REG 2019/6 defines that the PSMF is "*describing in detail the pharmacovigilance system with respect to [the MAH's] authorised veterinary medicinal products*" .

[1] Art. 21 para. 1 IR 2021/1281 specifies that the description "*shall […] reflect the pharmacovigilance system in place*." [2] Therefore, one can anticipate that the authorities grant a central place to the PSMF when it comes to pharmacovigilance inspections. Indeed, Art. 126 REG 2019/6 foresees that competent authorities and EMA shall conduct a regular check of the PSMF maintained at the company with the aim to "*ensure that […] the pharmacovigilance systems are being correctly applied*." [1]

The PSMF is maintained at the MAH, and only the summary is submitted to the competent authorities, which contains a reduced level of information. Therefore, Art. 76 para. 6 REG 2019/6 confers the right to the authorities to request the complete PSMF in order to conduct their check: "*The competent authority or the Agency, as applicable, may at any time request the marketing authorisation holder to submit a copy of the pharmacovigilance system master file*." [1]

2.1.2 PSMF location and Supervisory Authority

The Supervisory Authority is defined as the competent authority who will conduct the PSMF inspection as per Art. 126 REG 2019/6: it is the competent authorities of the Member State in which the PSMF is located. [1]

Therefore, there are important rules to consider when defining the location of the PSMF. As per Art. 25 para. 1 IR 2021/1281 "*the pharmacovigilance system master file shall be located in the Union at the site where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site where the qualified person responsible for pharmacovigilance operates.*" [2] VGVP on PMSF further specifies that:

- *"each PSMF can be only declared in one location"*
- the address of the location should be "*a physical address*"

– *"in the situation where the main activities take place outside the EU, or where a main site cannot be determined, the location should default to the site where the QPPV operates."* [5: section 2.3.1]

For international companies operating globally, these rules require careful attention for practical reasons: in case of inspection, the company should be in the position to provide adequate resources and support during the inspection at the site their PSMF is located in EU.

VOL 9B assigned inspection responsibility to "*the NCA […] in whose territory the MAH's QPPV is located*." [4: part I.2.5.1] Art. 126 para. 5 REG 2019/6 aims at *"[…] avoid[ing] the duplication of inspections of pharmacovigilance systems"* and encourages authorities to collaborate and "*enter into any work-sharing initiatives and delegation of responsibilities with other competent authorities*". [1] During a webinar held on 8th December 2021, Calogero Canavo from the Inspection Office, Quality and Safety of Medicines, presented on behalf of EMA what the cooperation between the national authorities will look like. There will be inspections programs at different levels to ensure coverage of the MAHs:

– A Centrally Authorized Product program will inspect PSMF of MAHs with CAPs in their portfolio, on request of CVMP. Executing authority will be the Supervisory Authority.

– National inspection programs will cover PSMF of MAHs with no CAPs in their portfolio. Executing authority will be the Supervisory Authority. [14: slide 22]

However, consideration should be given to the fact that beside of the QPPV, also the local PV representatives or any 3rd party "*carrying out pharmacovigilance activities in whole or*

in part, on behalf of or in conjunction with marketing authorisation holders" can be subject to a PV inspection, as specified by Art. 26 para. 1(c) IR 2021/1281. [2] I.e. inspections outside the scope of the PSMF, conducted by the Supervisory Authorities, are possible. And Mr Canavo stated in his presentation that triggers for inspection by non-supervisory authorities could be: to: "*verify compliance and/or product specific issue with national and EU requirement, [or] follow up at inspection findings upon request from the supervisory authority or another MS*". [14: slide 14] Therefore it is expected that national authorities from Member States will continue their inspection program of affiliates from international companies operating on their territories, even if they are not the Supervisory Authority for this MAH as per REG 2019/6 definition.

2.1.3 PSMF as tool to define the inspection program using a risk-based approach

The VGVP on inspections details how authorities shall proceed to determine their inspection program and with which frequency they will inspect a company.

First of all, "t*he establishment of inspection programmes will ensure that Marketing authorisation holders' pharmacovigilance system master files and the respective pharmacovigilance systems are inspected regularly, and that the inspection frequency is adjusted following risk-based approach in accordance with the factors in section 2.2 of this Module*." [6: section 2.4]

Factors to be taken into account for the planning of an inspection are related to:

- Inspections (e.g. previously identified compliance issues)
- Product (e.g. product(s) with additional pharmacovigilance risk-management measures)
- MAH (e.g. changes in MAH like merger or acquisition)

– PV system: factors related to the pharmacovigilance system are detailed in table 5, with the correspondence to the sections and annexes of the PSMF where inspectors can find the necessary documentation. [6: section 2.2]

Table 5: pharmacovigilance system related factors of risk and the emplacement of the potential information in the PSMF

Pharmacovigilance system related factors [6: section 2.2]	**Emplacement of the potential information in the PSMF**
"Marketing authorisation holder with sub-contracted pharmacovigilance activities (function of the QPPV, reporting of safety data, sub-contracting of pharmacovigilance system master file management, etc.)"	Section F Annex V.1 Specifically related to the function of the QPPV, further information are available in: • Annex V.2 • Annex II.4
"Third parties employed to perform pharmacovigilance activities"	Section F Annex V.1 and V.2
"Change of QPPV since the last inspection"	PSMF summary* Annex I: Logbook
"Changes to the pharmacovigilance database(s), which may include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data"	PSMF summary* Section D Annex I: Logbook
"Changes in contractual arrangements with pharmacovigilance service providers or of the sites at which pharmacovigilance is conducted or in pharmacovigilance system master file management"	Contractual arrangements with service providers: • Section F • Annex V.1

Pharmacovigilance system related factors [6: section 2.2]	Emplacement of the potential information in the PSMF
	Sites at which PV is conducted • Section C • Annex III.4 • Annex I: Logbook PSMF location: • PSMF summary* • Annex I: Logbook
"Other information available (e.g. assessment from other regulatory authorities in EU and outside EU)"	Outstanding findings related to audits and/or inspections: • Section E • Annex IV.6

* Change to the PSMF summary leads in addition to the submission of a variation not requiring assessment.

Based on these criteria, it is expected that any variation submitted in relation with the summary of the PSMF will raise the attention of the competent authorities. This is not new and was already the case in the past with the DDPS. Changes to the DDPS were mandatorily submitted as a variation, and the modification to the PV system as listed in table 5 were already known triggers for a PV inspection. [4: part I.2.5.3]

The focus on the sub-contracting of PV activities is not new either. The novelty resides in the level of details available to the authorities in one place and one document. For example, the annex V.1 provides the list of service providers: beside the type of PV tasks outsourced, the number of providers listed, their names and location, may play a role in the decision to inspect.

2.1.4 Information contained in the PSMF and inspection conduction

The PSMF also supports the preparation of the inspection itself, its scope and agenda. Reference is made to VGVP on inspections, section 2.7. [6]

Main items of a routine inspection are:

- *"Collection, reporting and recording of suspected adverse events for veterinary medicinal products […],*
- *Continuous benefit-risk balance monitoring […],*
- *PV system […]."* [6: section 2.7.1]

For the last item, the reading of the PSMF provides a sound and comprehensive picture of what is applied for PV activities in the company. MAHs should be aware that the starting point for the inspection will slightly shift in the future, and this will impact the inspection preparation and the inspection itself. For example, when inspectors were asking for a list of service providers in preparation to their inspection, they may now request copies of contract for selected 3rd parties because the list is already available to them in the PSMF. And during the inspection, they may directly go into the details of the wording used in the respective contract(s). Furthermore, the organization of the document itself, with main part and annexes, provides more possibilities to cross-check information beforehand. For example, between the section B on QPPV, the annexes II and V, there is a comprehensive view of any delegated and/or outsourced QPPV responsibility, and the inspection may start straight away on how the delegation is organized, documented and monitored.

The logbook is also an important source of information about the state of the PV system. At a glance, inspectors can appreciate the changes made to the PV system over the years, how stable the PV system remains in the company, and catch up on recent changes they

may want to dig into during the inspection. MAHs should prepare to provide explanations and documentations related to these changes.

The results of a PV inspection will be recorded in the Union Product Database, as stipulated in Art. 126 para. 6 REG 2019/6, and made available to the national authorities only.

2.2 THE PSMF AS INSTRUMENT FOR THE OVERSIGHT OF THE PHARMACOVIGILANCE SYSTEM AND ITS ACTIVITIES BY THE QPPV

The PSMF can be more than just a document maintained and compiled for inspection purposes. It can be a useful tool for the MAHs and their QPPV to keep the oversight on the PV system and its activities. EMA shared this view with the industry during a recent webinar dedicated to the PSMF on 08th December 2021. [12: slide 28] The following sections aim at demonstrating advantages and limitations of the PSMF while speaking about QPPV oversight.

2.2.1 One place to find current information on the PV system and its activities

Annex II : Oversight of the QPPV presents a comparison between the PSMF content as per IR 2021/1281 and the items a QPPV shall have oversight on according to the REG 2019/6. It is to note that there is a fast complete overlap between the content of the PSMF and the items the QPPV shall have oversight on.

The advantages of the PSMF for the QPPV are:

- The appreciable level of details of the document
- The availability of the information at one single place, in a structured manner
- The regular update of the information (see section 3.)

I.e. the QPPV can view extended and up-to-date information on the PV system and its activities at a glance. And the QPPV accesses in one place information which is usually spread over several systems within a company and not necessarily owned by the pharmacovigilance department. This information was in many cases already available to the QPPV, on an ongoing basis or upon request. However, the creation of the PSMF ensures an organized and systematic availability of the data.

Art. 78 REG 2019/6 provides a long list of tasks that the QPPv is responsible to ensure. [1] Beside a sound delegation process, the QPPV needs instruments to steer and monitor that the tasks are performed in a complaint manner. The annexes IV of the PSMF provide helpful information to steer the PV system and monitor its compliance and efficiency like the Key Performance Indicators, the open audit findings, the risk minimization measures.The logbook is an efficient tool to capture important changes to the PV system, including the open findings. The QPPV can follow up on the implementation of improvement measures to the PV system.

At the end, the same items that support an PV inspection preparation and conduction can support the oversight of the PV system by the QPPV.

2.2.2 Limitations

The PSMF is suitable for the QPPV's oversight to a certain extent. The following sections present aspects that MAHs may consider for further developments, but that go beyond the regulatory requirements.

2.2.2.1 List of audits with outstanding critical and major findings (Section E, annex I: logbook and annex IV.2)

The QPPV is informed on any major or critical findings arising from an audit via the Section E and the annex IV.2, that both capture the list of audit associated with unresolved critical or major findings. The difference between the two items in the PSMF is small: while only audits with outstanding findings should be listed in section E, annex IV.2 will

encompass all audits, highlighting those for which there are outstanding major or critical findings. [2]

Any new audit resulting in critical or major findings will be added to the two lists. Furthermore, because section E is modified, the changes will be captured in the logbook, and will spot the new issues detected within the PV system at a glance.

Annex IV.2 offers further useful information to the QPPV, especially those facing international organizations:

- all scheduled audits are listed, and the progression of the audit plan becomes visible

- the QPPV can put in relation how many audits result in critical or major findings with those that only generate minor findings and observations. This helps to distinguish between system-relevant issues and local, spotted problems.

However, the QPPV should also be aware of any delayed implementation of corrective and/or preventive measures for the critical and major findings, as well as the justification thereof. This is not captured in the PSMF.

In the PSMF for human pharmaceutical companies, Good PV Practice module II expected "*[…] to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s).*" [15: section II.B.4.7] This level of details is not required in the PSMF according to IR 2021/1281 [2], however could provide a guidance for companies looking into providing a more robust oversight to their QPPV with that regard.

2.2.2.2 Capture of changes

Having information on the current status on the PV system at one given time, like a frozen picture, is not sufficient for a full and efficient oversight. The dynamic aspects are missing that are important to the QPPV to be able to react in timely and appropriate manner to issues, or even better to anticipate improvements needed in the PV system. The QPPV needs to know what changed with the recent update of the PSMF. Only changes to the main part of the document will be captured in the logbook (annex I of the PSMF), which includes the list of open findings though. But "*changes to the information in the Annexes do not need to be tracked in the form of a logbook […].*" [5: section 2.3.3]

For example, the list of all MAs held by the MAHs (i.e. annex III.1of the PSMF) is of little support for the QPPV. The QPPV needs to understand which newly authorized products are now under his/her responsibility, and which new product should be included into the signal management program for the monitoring of the benefit-risk profile. In case of a new authorization or updated authorization expanding the scope of utilization of an existing product (e.g., new indication, new species), the PV teams should expect an increased volume of adverse events due to a higher awareness on the product following the marketing activities to promote it. The QPPV should be aware of such events and anticipate their possible impacts on the PV system.

Similarly, the QPPV should be kept informed about:

- New or updated contractual and sub-contractual arrangement signed with 3rd party (annex V.1 and V.3 of the PSMF). The QPPV needs to be aware of new outsourced PV activities, and any modification of the services specifications, that may impact the quality of the PV activities.

- New or updated procedure (annex VI.1 of the PSMF). The QPPV needs to be aware of the processes in place to perform the PV activities he/she is responsible to ensure, and when they change.

– New risk minimization measures and/or changes in their outcome (annex IV.6 of the PSMF). Obviously, the QPPV shall know about new signal validated for one of the products covered by the PSMF and the measures agreed upon, i.e. the QPPV should be made aware about any new entry to the list in annex IV.6.

The QPPV is for sure involved in activities like the review of the PV agreements and procedures, and in discussions related to signal validation and risk minimization measures. However, depending on the size of the company, delegations may be in place. In addition, the volume of information received by the QPPV may just exceed the capacities that a human is able to remember.

Companies who want to efficiently use the PSMF as a tool for the oversight of their QPPV should create the missing content and display it in appropriate manner to their QPPV. For example, in building up the changes between two subsequent versions of the same annex: the annex III.1 could be augmented by a list of new and modified MAs. Processes are usually in place at MAHs to provide the QPPV with dynamic information related to the PV activities (e.g., KPIs), for example via dashboard. While implementing the new process to maintain the PSMF, MAHs should figure out how to connect and include this maintenance activity into existing practices and tools in the company, and how to display the information on changes In the PSMF to their QPPV.

2.2.2.3 Post-marketing surveillance studies

There is no specific annex dedicated to the post-marketing surveillance studies in the PSMF. And REG 2019/6 abolished the PSUR, aggregate report which contained a specific section related to completed studies and the safety information received out of them.

REG 2019/6 introduced the requirement to collect and report to the Union Pharmacovigilance Database any adverse event from a solicited source. However, a pharmacovigilance

database, at MAH or at EMA, is not designed to collect information on the studies themselves: no information is captured related to the study conduction, when it will start and end. If no Adverse Event is reported out of the study, the early detection of an eventual under-reporting is challenging. In other words, the collection of adverse events from solicited sources does not provide an adequate mechanism for the oversight of the QPPV on post-marketing surveillance studies.

In consequence, and in order to maintain the oversight on these activities as per Art. 78 para. 1 REG 2019/6 [1], the QPPV needs a separate process. Companies may consider to align and/or include this process to the one established for the maintenance of the PSMF.

2.2.2.4 Communication to authorities

No link or interaction is foreseen between the PSMF and the way MAHs communicate to authorities on their product profile, in particular the communication plan.

The QPPV should be involved in any communication to the authorities s per Art. 78 para. 1 REG 2019/6 [1]. However, it would be beneficial if the QPPV could also access information on past communication for safety purposes in a collated and organized manner, across all regulatory procedures, when discussing and reviewing a new document. Past experience from the author demonstrates that it could be challenging to keep oversight, when the safety information was communicated in parallel as answers to the PSUR assessment, but also as answers to List of Questions in the scope of a variation procedure. The latter was usually steered outside of PV by the Regulatory Affairs department, and filed or archived outside of PV (e.g. in the Regulatory Information Management system).

The author sees some advantages for the QPPV's oversight in the new notification system for validated signals. All notifications should be performed in IRIS, a database maintained by EMA that is used for the notification of signal. However, the tool does not offer any reporting functionalities yet, that would allow MAHs to extract information on the notifica-

tions made. Therefore, MAHs should rely on internal systems and processes to keep oversight on what has been communicated by when to EMA and competent authorities.

2.2.3 Scope of the data

There is no direct statement related to the scope of the data to be delivered, neither in REG 2019/6 nor in IR 2021/1281. [1, 2] The VGVP on PSMF states that "*the content of the pharmacovigilance system master file should reflect availability of global safety information for veterinary medicinal products authorised in the EU, presenting information on the pharmacovigilance system applied at global, regional and national level, as applicable*." [5: section 2.3.2] Therefore, MAHs could decide to limit the information provided in their PSMF to products authorized in the EU.

However, internationally operating companies usually have worldwide organized PV systems, using the same processes and repositories for their data. Excluding data for non-EU authorized products may require additional preparation steps that are of little value.

3 IMPLEMENTATION OF THE PSMF

3.1 SURVEY

The last part of this master thesis will present the requirements and challenges linked to the creation and the maintenance of the PSMF. It is sustained by information and responses gained via a survey sent to companies that are members of Animal Health for Europe and the Bundesverband der Pharmazeutischen Industries. Annex III: Survey – forms provides the survey form circulated, and Annex IV: Survey – results the results in tabulated format.

3.1.1 Descriptive presentation of the results of the survey

Eight (8) companies answered the survey, six (6) large companies and two SMEs. From the eight (8) companies, three (3) operate only in the European Union, all the others conduct a worldwide business (n=5). All companies who answered have their QPPV in-house.

From the eight (8) companies, only two (2) stated to have had only a draft for the PSMF ready by 28. January 2022, when REG 2019/6 came into force. However, from the six (6) companies claiming to have their PSMF ready by 28. January 2022, four (4) stated that the challenges they encountered during the compilation of the annexes have an impact on the document generated, either because of the reliability of the data included (n=3), of the quality of the data (n=3) or because the document produced was potentially incomplete (n= 2). it is to note that one (1) company did not detail which challenges has impacted the document generated.

To create the main part of their PSMF, five (5) companies could reuse approximately 50% of the content from their DDPS, while the remaining three (3) could even reuse 80% of this content. Five (5) companies consider that the description of their PV system in the main part of the PSMF (section A to F) is more detailed than it was in the former DDPS, because the adaptation required to comply with the requirements from the IR 2021/1281. Interestingly, there is no relationship between the fact of reusing only 50% of the DDPS to create the PSMF main part and the appreciation of the level of details to be higher. Two (2) companies lower the level of details provided for the description of the PV system in their PSMF, because they strive for the main part to remain relatively constant, and because they are waiting for some lessons learned from upcoming inspections.

The annex causing challenges to the majority of companies is the annex V.3, list of contracts with 3rd party, cited by five (5) respondents, followed by annex III.1, list of marketing authorization, annex IV.1, list of procedural documents and annex IV.2, list of audit with outstanding findings (n = 3 for each). The respondents also mentioned the annex III.3, list of local representative and the annex IV.5, dose factor (n=2 for each), the annex I, logbook, the annex IV.3, list of KPIs, the annex IV.4, information on trainings, the annex IV.6, list of risk minimization measures, and the annex V.1, list of activities outsourced (n=1 for each).

As most frequent reason for the challenge, the companies point out that the existing tracking and electronic systems in use to store the information required are not designed

to deliver it (i.e. no or limited reporting functionalities) (n = 12). Companies also complained about the lack of cooperation of interacting departments owning the data with PV (n=6) and about the availability of the data at one single point within the company (n=5).

Regarding the maintenance, only one (1) company does not intend to update the PSMF created during 2022. The other companies prefer either to wait for more guidance (n=3), or plan an update after 6 months (n=2) or every quarter (n=2).

All companies but one (1) have developed a process how to generate the annexes as they create them. The logbook is a manual exercise according to four (4) companies, while two (2) rely on a semi-automated process and one (1) hopes for an upcoming electronic system that generates the logbook automatically. Two (2) companies expect the departments owning the data to provide an overview of the changes in comparison to the previous version.

The companies plan in their vast majority to dedicate less than an half 'Full Time Equivalent' to the maintenance activities for the PSMF (n= 7) and none of them intends to outsource those maintenance activities.

3.1.2 Discussion

The sample of companies that respond to the survey is quite small. Furthermore, this sample is not well balanced with a majority of companies having large organizations operating worldwide. Therefore, the survey cannot claim to be representative for the challenges and efforts deployed by companies to generate their PSMF, and may only show a few trends. They will be discussed in the following.

3.2 CREATION OF THE FIRST VERSION: CHALLENGES AND STRATEGIES

3.2.1 Novelty

As demonstrated in the first part of this master thesis, the PSMF is a completely new document, in its concept and its contents. It is much inspired by the document required for human pharmaceutical companies, and MAHs with contact and/or experience in the current human pharmaceutical legislation, including GPV, certainly have an advantage.

The PSMF is one novelty amongst others, that MAHs of veterinary products in Europe face with REG 2019/6. Beside the PSMF, the implementation of VICH HL7 format for the submission of adverse event reports to the Union PV database, the reporting of all adverse events to the Union Pharmacovigilance database within 30 days, and the new signal management process are highlights of the new veterinary regulation [1, 2]. The projects necessary for their implementation compete very much for the limited resources in PV departments. The introduction of the Union Product Database mobilizes also important resources within companies. MAHs may have prioritized their efforts, and dedicate less resources and time to the PSMF.

Nevertheless, this novelty does not seem to have prevented companies from creating their first version of the PSMF on time for the implementation date of REG 2019/6. The responses to the survey give a few trends with regards to the strategy that may have been adopted:

- the description of the PV system in the former DDPS have been reused to 50 to 80%, saving time for the creation of the main part

- companies are aware of gaps in the PSMF created, either from a content or qualitative point of view, and seems to accept the risks for now.

Although not questioned in the survey, it is expected that companies have documented the potential gaps they are aware of, can explain the rationales of those gaps during an inspection and have plans to close the gaps in the future.

3.2.2 Availability of the secondary legislation

The PSMF is roughly described in REG 2019/6, which was published in 2019. However, the secondary legislation was released rather late prior to the date REG 2019/6 was coming into force: the IR 2021/1281 was published in August 2021, and the VGVP module on PSMF in November 2021. It leaves less than six months to the companies to generate a PSMF that is compliant with the regulatory requirements. No transition period was considered REG 2019/6, all provisions shall be followed by 28. January 2022 [1: Art. 153, 154 and 160], and therefore authorities were expecting the PSMF to be readily available after 28. January 2022 [12: slide 23].

It is to note that according to the author's experience, inspectors apparently acknowledged the challenges of the situation. In a request for submission of the PSMF received during the first quarter of 2022, the inspectors gave a deadline of one month for the MAH to provide the PSMF, instead of the 7 days foreseen in REG 2019/6 [1: Art. 79, para. 6].

Furthermore, it seems that the details provided in the secondary legislation is not fully sufficient for MAHs to build up their PSMF. Many companies respond in the survey that even if they had their PSMF ready by 28. January 022, they are now awaiting for further guidance, for example from lessons learned during upcoming inspection(s), prior to updating the first created version of the PSMF, main part and annexes. There is a lot of uncertainties in companies related to the PSMF.

3.2.3 Availability of the data within the company

In the first part of this master thesis, the correspondence between the former DDPS and the PSMF was discussed. When the DDPS can deliver the basis for the main part of the PSMF, as confirmed by the survey, many additional data have to be provided in the an-

nexes. The challenge of the annex compilation resides in the availability of the data within the company. This is also confirmed by the survey, with a clear trend reporting issues with the existing electronic systems: those are not able to deliver the information required. For example, the system may initially not support the extraction of information but rather the use of workflows, the documentation of decision-making, and the archiving of documents. It implicates to develop and validate new queries or report functionalities, which necessitates the involvement of the Information Technology department, the vendor of the system and time-intensive validation processes.

Companies also reported on having issues with the data availability within the companies at one point. They are most likely spread within different electronic systems and repositories, outside of the PV department and owned by other departments (e.g., audits within a QA document management system, contracts in a database managed by the Legal department). In addition, companies complained that interacting departments and data owners may not well cooperate with PV to gather the data. The PV departments needs to include all stakeholders, e.g., Regulatory Affairs, Quality Assurance, Legal, in presentation and discussion around the PSMF. It takes time to convince those stakeholders, and even they are convinced, they may not be in the position to prioritize the delivery of data for the PSMF.

Companies may also face the need to establish global repositories and collate the data first, prior to be able to generate the required annex. The best example is the annex IV.5 on dose factors: the information is available in the former PSURs though, but needs to be collated at one place, product per product, in a manual effort.

It is to note that according to Art. 22 para. 3(c) IR 2021/1281, MAHs are required to create a list of their Marketing Authorizations containing the International Non-proprietary Name (INN) as a data field [2]. This is not consistent with the data structure used for the UPD [13]. The concept of INN is rather used in the PSMF for human pharmaceutical products [15]. In its position paper from 8. June 2021, Animal Health for Europe expressed concerns related to providing a list of all Mas hold by the MAH, but did not comment

specifically on this detail of IR 2021/1281 [16: section 2.3]. One may rather consider to list the active substance(s) like in the UPD.

3.3 MAINTENANCE PROCESS WITHIN THE COMPANY

3.3.1 Accuracy and completeness of the data

PV inspections have the aim to check the "*Accuracy, completeness and maintenance of the pharmacovigilance system master file*." [5: section 2.7.1]

For the maintenance of the PSMF, it means that the information presented should reflect the current state of the PV system and be reliable. In general, data extracted from validated systems should be considered more accurate and reliable than data compiled manually, and manual compilation should include a review step to ensure the quality of the data. When the information is provided by stakeholders within the company, they should ideally ensure the PV teams that the data in the systems they control are complete, and that the systems are supported by a sound maintenance process. It is recommendable to document known gaps in company's systems, incl. remedies in place or scheduled. This documentation is not part of the PSMF, but should be kept aside of the PSMF files as part of the Quality Management System applied to PV (reference is made to section 1.5.1 for details).

3.3.2 Updates

3.3.2.1 Frequency

Art 24 para. 1 IR 2021/1281 states: "*Marketing authorisation holders shall keep the pharmacovigilance system master file up to date and revise it, where necessary, to take account of experience gained, and of technical and scientific progress*." [2] This is the direct consequence of the expectation for the PSMF to present complete and accurate data reflecting the current PV system. [2: Art. 21 para. 1] Obviously, certain types of information collated in the PSMF, especially in the annexes, are subject to frequent changes, e.g., the marketing authorizations held by the MAHs, the list of written procedures, and will require update.

There is no further definition neither in IR 2021/1281 nor in the VGVP module on PSMF on what is 'up-to-date', and what would be an acceptable frequency for the update. The same requirement is applying for the PSMF of human pharmaceutical companies. [15: section II.B.5] Therefore it can be considered appropriate to follow the standard established for the human pharmaceutical companies' PSMF since 2012 and accepted by the PV inspectors: quarterly update. An update every three months provides sufficient confidence that the information presented is reflecting the current status of the PV system. Furthermore, the regular update of the PSMF and its annexes will bind resources within the PV departments and a quarterly update is also a fair compromise to keep the administrative burden to an acceptable level. Interestingly, only two (2) companies participating in the survey were planning to update their PSMF every quarter. However, this may change once more clarity and guidance are available to the MAHs on the expectations from PV inspectors.

All the annexes may not require an update every quarter. Table 6 proposes a grouping of the annexes in items changing rather frequently or occasionally. For the annexes changing on particular occasions, the MAHs may envisage an ad hoc update of the annex.

Table 6: PSMF annexes grouped by items that change rather frequently or occasionally – a proposal

Annexes with items changing frequently*	Annexes with items changing occasionally*
Annex III.1: *a list of all veterinary medicinal products covered by the pharmacovigilance system master file*	***Annexes II:*** *additional information regarding the qualified person responsible for pharmacovigilance, assistant veterinary surgeon, and associated back-up arrangement*
Annex IV.1: *a list of documents, policies, procedures and processes used for the pharmacovigilance activities referred to in Article 4(3), (4), (5) and (6)*	***Annex III.2:*** *a list of reference numbers for other pharmacovigilance system master files held by the same marketing authorisation holder, where applicable*
Annex IV.2: *a list of all scheduled and completed audits including outstanding critical and major findings*	***Annex III.3:*** *a list of local or regional representatives for the purpose of receiving reports of suspected adverse events, including*

Annexes with items changing frequently*	Annexes with items changing occasionally*
	their contact details, responsibilities and territories, where applicable
***Annex IV.4**: the information on training plans and records referred to in Article 6(2)*	***Annex III.4:** a list of the sites where pharmacovigilance activities listed in Article 4(3), (4), (5) and (6) are carried out*
***Annex IV.6**: a list of risk management measures and the outcome of risk minimisation measures;*	***AnnexIV.3**: a list of performance indicators and how to use them, as referred to in Article 7, as applicable*
***Annex V**: further information on contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities*	***Annex IV.5**: the methodology to calculate the factor referred to in Article 14(2);*

* Annexes' names as listed in IR 2021/1281 [2]

3.3.2.2 Impact of a regular update of the annexes

After having updated the annexes, during a regular update iteration or in an ad hoc manner, the MAH should check for any impact on the information presented in the main part of the PSMF. For example, modification to the list of audits with outstanding findings presented in annex IV.2 should be checked for impact on section E, where similar information is provided. MAHs updating the main part should also remember to describe the changes made into the annex I-logbook of their PSMF.

According to the survey, only few companies see opportunities to automate this check, and the update of the logbook in the future; for most of them, it remains a manual activity, with the administrative burden linked to manual process in a GxP regulated environment (e.g. audit-proof documentation).

3.3.3 Filing and archiving

3.3.3.1 Version control

As per Art. 24 para. 23 IR 2021/1281, the MAHs shall implement processes to document and track the regular updates performed: "*The pharmacovigilance system master file shall be subject to version control and indicate the date when it was last updated.*" [2]

In order to track changes made to the main part of the PSMF, Art. 24 para. 24 IR2021/1281 creates the Annex I or logbook, where "*Marketing authorisation holders shall record in a logbook any alteration to the content of the main part of the pharmacovigilance system master file made within the last 5 years. Marketing authorisation holders shall indicate in the logbook the changed section, the kind of change, the date, the person responsible and, where appropriate, the reason for the alteration*." [2]

There is no need to track changes to the annexes in the logbook, but a robust tracking process, external to the PSMF, is expected, as detailed in the VGVP on PMSF: "*The information and superseded versions of such content [i.e. Annexes of the PSMF that are regularly updated] may be managed outside of the PSMF content itself, provided that the history of changes is maintained and available to competent authorities and the Agency on request.*" [5: section 2.3.3]. The tracking process should have two purposes:

- the oversight on the latest updated version of each single annex of the PSMF
- the retrieval of former versions, to document the historical changes

Many companies participating in the survey plan to use a dedicated electronic tool to manage the filing and archiving of the single parts (ie. main part,annexes) of their PSMF, partly because they have such a tool (e.g. electronic DMS) at their disposal. This is certainly the most robust solution that companies can implement, and it will ensure a high degree of compliance with the regulatory requirements described above.The MAH should remember to describe this electronic system in the PSMF under the section D of the main part, to create a procedural document describing the filing of the PSMF in this system and to include the reference of this procedural document in the annex IV.1 of the PSMF.

3.3.3.2 Further requirements

Art. 25 para. 2 IR 2021/1281 states in addition: "*The pharmacovigilance system master file may be stored or made available in electronic form. The media used for storage or making available shall be searchable and shall remain readable over time.*"

Electronic DMS usually satisfies these requirements. However, when companies do not have an electronic DMS or cannot use it for the PSMF but want to keep the PSMF in an electronic form, they should consider alternative strategies. For example, when the PSMF should be kept in organized files, companies should consider to:

- use a granular folder structure and sound naming conventions for the annexes, supporting the navigation
- keep superseded versions separated from the current valid ones
- systematically compile the complete PSMF after each iteration update (see section 3.4)

3.3.4 Publication of the PSMF for submission

Authorities and PV inspectors may require a copy of the logbook or any other part of the PSMF to be submitted to them within seven calendar days, as per Art. 24 para. 5 IR 2021/1281. [2] It is an extremely short time given the size and the complexity of the document. The VGVP module on PSMF insists on the fact that "*Marketing authorisation holders need to ensure that the obligations concerning the timely provision of an up to date PSMF can be met.*" [5: section 2.3.3] For this reason, the author recommends a regular update of the annexes and the main part of the PSMF, in order to have up-to-date documents by hand that can easily be compiled together. The systematic compilation of the psMF after each iteration update may also be an advantage, the requested document being readily available for submission.

However, MAHs may also consider to update a few annexes in an ad hoc manner prior to publication and submission to a competent authority. Rationales for the decision to update in an ad hoc manner include but are not limited to:

- a newly launched product, that triggers the PV inspection, was not included in the last version of annex III.1, list of MAs;
- CAPAs for major or critical findings have been completed since the last update of annex IV.4;
- important organizational or personal changes took place since the last update and impact the description of the PV system in section C and/or annexes III.2, III.3, III.4;
- a recent outsourcing of PV activities is not captured in annex V.1;

The limiting factor to any ad hoc update is the time, as there are only seven calendar days to gather the updated data, and collate the full PSMF into one document. The QPPV should be involved in the decision.

When the PSMF is maintained electronically, the creation of a print copy should be possible as per Art. 25 para. 3 IR 2021/1281. [2] Furthermore, VGVP module on PSMF points out the need for navigation support through the document: "*The content shall be indexed to allow for efficient navigation in the document.*" [5: section 2.3.2] The use of the Portable Document Format (PDF) is probably the easiest way to satisfy these requirements at the moment: main part and annexes in different formats (e.g. Microsoft Word, Microsoft Excel) can be transformed in PDF and compiled together, bookmarks and hyperlinks can support the navigation through the document. However, the administrative burden to compile such a PDF compiling is not negligible. According to the author's experience, it takes minimum one hour. For certain annexes (e.g. list of MAs, list of 3rd party), the PDF format is of limited value and restrains the functionalities usually available in the original

format (e.g. filtering function, pivot table in Microsoft Excel). It is expected that PV inspectors will request the separate submission of annexes in a searchable format in addition to the compiled PSMF. MAHs may consider to protect the data of such annexes from corruption, or unintended deletion, for example by using a password.

The requirements for publication of the PSMF for submission purposes add quite of a burden of the PV teams maintaining the document. The modern world would offer other solutions to safely share access to a document maintained electronically (e.g. Microsoft Share Point). The recent pandemic has shown companies making huge steps toward a paperless office, which is also beneficial to our environment. This was commented by Animal Health for Europe in its position paper from 8. June 2021, but the requirement was kept in the final version of IR 2021/1281. [16: section 3.8]

3.4 INTRODUCTION WITHIN THE MARKETING AUTHORIZATION DOSSIER

3.4.1 Creation of the PSMF summary

As presented in section 1.2.1, only a PSMF summary is now included in application dossiers for marketing authorization. [1: Art. 8, para. 1(c)] Art. 23 IR 2021/1281 describes the content of the PSMF summary:

- *"(a) the pharmacovigilance system master file reference number;*
- *(b) the pharmacovigilance system master file location*
- *(c) name, contact details and place of operation of the qualified person responsible for pharmacovigilance*
- *(d) the signed statement referred to in Article 22(2)(b), point (I)*
- *(e) the type of record management system used for adverse events reports including the name of the database, if applicable*." [2]

The PSMF summary is reduced to administrative information related to the MAH and its PV system. Although not specified in IR2021/1281 it is recommendable to apply the same version control principles to the PSMF summary than to the PSMF itself. Furthermore, it should be easily available to the Regulatory Affairs teams in charge of marketing authorization submissions.

3.4.2 PSMF summary and the Union Product Database

Some information contained in the PSMF summary are included into the Union Product Database (UPD): the PSMF number, the PSMF location and the name and contact details of the QPPV.

It is to note that Art. 74 para. 1 REG 2019/6 foresees this information to be included in the Union Pharmacovigilance Database. [1] However, the Union PV Database would not offer any field to store this information. Finally, this requirement is met via the interface between UPD and the Union PV Database as established in Art. 74 para. 2 REG 2019/6. [1]

The creation and population of the UPD is under the responsibilities of the NCAs. The MAHs are asked to either forward the information on their PSMF and QPPV to the NCAs directly or to submit a Variation Not Requiring Assessment (VNRA, see section 3.4.3). [17: question 25]

3.4.3 Variation Not Requiring an Assessment (VNRA)

The annex to Implementing Regulation 2021/17 lists the variations for which an assessment by the NCAs is not considered necessary. A VNRA shall be submitted in relation with the PSMF for the following topics:

- change in name and/or contact details of the QPPV (C.1)
- change in location of the PSMF (C.5)
- introduction of the PSMF summary in replacement of the DDPS (C.6) [18]

It means that within 30 days after the item was changed in the company, the authorities should be notified per VNRA. There is no need to wait for an approval by the authorities to make the changes. The companies are more flexible in the implementation of important changes in relation with the PSMF and their PV system, and the time they decide to implement those. The VNRA also lower the administrative burden in Regulatory Affairs teams, in comparison to the submission of a variation Type IB for any modification made to the DDPS.

4 DISCUSSION AND CONCLUSION

One aim of REG 2019/6 was the announced reduction of the administrative burden for veterinary pharmaceutical companies in general. Is this goal achieved with the PSMF?

To some extend yes and certainly, the introduction of the PSMF summary in the replacement of the DDPS in authorization dossiers as well as the introduction of VNRA to notify changes to the PSMF summary is an important relief for the Regulatory Affairs teams in the companies. Only some key information related to the PV system is variation-relevant and these variations will not require assessment by NCAs. However, companies should also consider the update of the Union Product Database for these key items in the future.

On the other hand, the extent of the information to be collected in the PSMF increases massively the workload of the PV teams. The DDPS was including less information, and this information was usually available within the PV teams and controlled by the PV departments. With the PSMF, the companies face new and major challenges to gather the requested data, which are in general not yet available at one point within the company and/or not with the required level of details. In many cases, the compilation of the data is still a manual effort. It impacts the PV teams but also other teams in the company. Data owners outside of PV (e.g. Regulatory Affairs, Quality Assurance) need to improve their own systems and processes to be able to provide the requested data. There is some hope that the current challenges will decrease with the time and the improvement of the company's systems, but this will take time and burn resources.

In comparison to the PSMF, the DDPS contained information that was quite stable over the time. Only important changes to the PV system would have triggered the update of the DDPS, while most of the PSMF annexes are prone to frequent changes (e.g. list of marketing authorizations, list of SOPs). Companies are required to continuously update their PSMF, if they want to comply with the regulatory requirements of being 'up-to-date'. The complexity of the modular structure requires the development of a special expertise within the PV team to deal with the PSM. The maintenance processes become

quite complex, due to the enormous requirements made in REG 2019/6 and its secondary legislation in terms of version control and publishing The PV teams need to keep track of each part of the PSMF that has been updated. The repository used should identify clearly the current versions, in order to secure a compilation of the PSMF into a single printable document within seven calendar days. Beside validated DMSs, there are currently only a few software solutions available on the market that could support the maintenance process of the PSMF as required. But those solutions will not be accessible to all veterinary companies, because of the IT infrastructure and costs related to their use.

It seems that in practice, the workload has been shifted from one team in the company (Regulatory Affairs) to the next one (PV). In addition, the extended information required and the maintenance process will require to allocate dedicated resources to the PSMF, which are not counterbalanced by the more convenient regulatory procedure.

The modular concept of the PSMF, with a main part supplemented by annexes, increases the flexibility in terms of process for the maintenance: selected parts can be updated when necessary. Companies can decide, using a risk-based approach, how often they will update which part of the PSMF. Envisaging a future where processes are more and more automatized, the structure of the PSMF opens interesting opportunities. For annexes that are extracted from validated electronic systems, the MAHs may consider semi- to full automated update of those annexes, reducing the workload of the PV teams in charge. A real time extraction of the data whenever they are needed, for a submission, during an inspection, for the QPPV, may become possible: the update would not follow an iteration process but occur on-demand. Automation can also support the capture of the changes between subsequent versions, in order for the PV teams to assess the impact on the main part of the PSMF. However, these possible opportunities require significant investment in time and money within the companies to implement the smart electronic systems needed. It assumes also that the competent authorities and their PV inspectors will accept to

follow the industry on this path and align their approaches during inspections. At this stage no one can predict the position of authorities and inspectors.

Because the administrative burden increased for PV teams to maintain a description of their PV system in the format of the PSMF, companies should look at the added values they can create with this document. The main purpose described in REG 2019/6 is the PV inspection preparation, which will not recur too often. [1] However, the information gathered in the PSMF and updated on regular basis can be useful for the QPPV. The second part of this master thesis showed the important overlap between the items a QPPV needs to have oversight on, and the information collated in the PSMF. Furthermore, this information is available in a standardized and organized manner, at one place. The development of semi- and automated update processes will also benefit to the QPPV, and make updated data easily available at any time for his/her oversight. Therefore the PSMF can and should be more than a document maintained for regulatory and inspection purposes.

It is to note that the data in the PSMF give a static picture of the PV system at the time the PSMF is updated. In addition, the PSMF provides limited insight into the changes over time, with exception of the logbook. Companies may take the opportunity of building new processes for the PSMF maintenance to go beyond the regulatory requirements and also capture the changes between subsequent versions of the annexes. This will help the QPPV to spot at a glance the new items in the PV system (e.g. newly authorized products, new audit findings). Because the PSMF did not fully overlap with the items to be under oversight of the QPPV, companies may also choose to embed additional tracking process (e.g. for clinical trials) into their iteration update of the PSMF.

Uncertainties remain at this stage about the expectations of authorities and PV inspectors in relation with the PSMF, its format, its content and the maintenance process. For example, it is unclear if a repeated update of the PSMF every three months will be considered in compliance with the requirements to have an 'up-to-date' document. Many questions

also arise along with the new items like the list of KPIs, the dose factors and the list of risk minimization measures. It will be interesting to observed the results of the first PV inspections, to be conducted assumably during the second half of 2022. It is to hope that at least trends and frequent findings will be shared with the companies soon in 2023.

SUMMARY

With the implementation of the Regulation (EU) 2019/6, veterinary pharmaceutical companies are requested to create and maintain a new document describing their pharmacovigilance (PV) system: the Pharmacovigilance System Master File (PSMF). The PSMF itself is maintained in house while a short PSMF summary, containing administrative information and a few key items of the PV system is submitted with the application dossier. Any changes to the PSMF summary are easily notified to Competent Authorities via Variation Not Requiring an Assessment and the Union Product Database is updated. Competent Authorities in the Member States are expected to inspect regularly that the description of the PV system in the PSMF is adequately applied within the company.

The PSMF has a modular format, with a main text part organized in defined sections and supplemented by several annexes. The PSMF should be up-to-date and therefore companies should develop and implement processes to update main part and annexes regularly. The regulatory requirements made in the Regulation 2019/6 and its secondary legislation are high:

- the content of the annexes reaches a high level of details
- the scope of the information goes far beyond the data usually owned by PV
- the regular update should be sustained by a sound filing process, including version control

The PSMF increases the administrative burden for veterinary companies. The requirements are going far beyond the former Detailed Description of the PV System (DDPS). However, it may be a valuable tool for the oversight of the QPPV on the PV system, and the efforts invested by the PV teams to create and maintain the PSMF can be rewarded in this way.

LITERATURE REFERENCES

[1] Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (URL: http://data.europa.eu/eli/reg/2019/6/oj, accessed 12 June 2022)

[2] Commission Implementing Regulation (EU) 2021/1281 of 2 August 2021 laying down rules for the application of Regulation (EU) 2019/6 of the European Parliament and of the Council as regards good pharmacovigilance practice and on the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products (URL: http://data.europa.eu/eli/reg_impl/2021/1281/oj, accessed 12 June 2022)

[3] EMA web-site presenting the veterinary medicinal products regulation (URL: https://www.ema.europa.eu/en/veterinary-regulatory/overview/veterinary-medicinal-products-regulation, accessed 12 June 2022)

[4] Volume 9B of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use (URL: https://ec.europa.eu/health/system/files/2016-11/vol_9b_2011-10_0.pdf, accessed 12 June 2022)

[5] Guideline on veterinary good pharmacovigilance practices (VGVP) - Module: Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files (18 November 2021 , EMA/595115/2021) (URL: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-pharmacovigilance-systems-their_en.pdf, accessed 12 June 2022)

[6] Guideline on Veterinary Good Pharmacovigilance Practices (VGVP) - Module: Controls and pharmacovigilance Inspections (18 November 2021,EMA/328998/2021) (URL: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-controls-pharmacovigilance_en.pdf, accessed 12 June 2022)

[7] Guideline on veterinary good pharmacovigilance practices (VGVP) - Module: Signal Management (18 November 2021 , EMA/522332/2020) (URL: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-signal-management_en.pdf, accessed 12 June 2022)

[8] Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (URL: ΓΠΜ// ∫∈Ε JPΞΛΜΕ JP/ J⊕Z∫Ε2001/82/ΛΖ, accessed 12 June 2022)

[9] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (URL: http://data.europa.eu/eli/dir/2010/84/oj, accessed 12 June 2022)

[10] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council (URL: http://data.europa.eu/eli/reg_impl/2012/520/oj, accessed 12 June 2022)

[11]Committee for Medicinal Products for Veterinary Use: Scientific recommendation for implementing measures under Article 77(6) of Regulation (EU) 2019/6 on veterinary medicinal products regarding the pharmacovigilance system master file from 29. May 2020 (EMA/CVMP/123178/2019) (URL: https://ec.europa.eu/food/system/files/2020-06/ah_vet-med_imp-reg-2019-06_mandate_art-77-6-psmf_ema-advice.pdf, accessed 12 June 2022)

[12] Mylona, S, on behalf of EMA, Veterinary Medicines Division, Inspection Office – Quality and Safety of Medicines: 'VGVP module on Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files' - presented during a webinar on 8 December 2021 (URL: https://www.ema.europa.eu/en/documents/presentation/presentation_en.pdf, accessed 12 June 2022)

[13] EU Implementation Guide (Vet EU IG) on veterinary medicines product data in the Union Product Database - Implementation of the requirements of Regulation (EU) 2019/6 for the Union database on veterinary medicinal products in the European Economic Area, Chapter 2: Format for the electronic submission of veterinary medicinal product information, Version 1.2 updated on 20. May 2022 (EMA/444352/2021) (URL: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/eu-implementation-guide-ig-veterinary-medicines-product-data-chapter-2-format-electronic-submission_en.pdf, accessed 12 June 2022)

[14] Cannavo, C., on behalf of EMA, Veterinary Medicines Division, Inspection Office – Quality and Safety of Medicines: 'VGVP module on Controls and Pharmacovigilance Inspections: Introduction and Principles' – presented during a webinar on 8 December 2021 (URL: https://www.ema.europa.eu/en/documents/presentation/presentation-vgvp-module-controls-pharmacovigilance-inspections-introduction-principles-calogero_en.pdf, accessed 12 June 2022)

[15] Guideline on good pharmacovigilance practices (GVP): Module II – Pharmacovigilance system master file, revision 2 from 28. March 2017 (EMA/816573/2011 Rev 2) (URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-

pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf, accessed 12 June 2022)

[16] Animal Health for Europe, Position Paper from 8. June 2021 on 'Good pharmacovigilance practice and the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products - Implementing Act of EU Regulation 2019/6 article 77(6)' (URL: https://ec.europa.eu/food/system/files/2020-12/ah_vet-med_imp-reg-2019-06_cons-fbk_del_art-77-6-psmf_ahe.pdf, accessed 12 June 2022)

[17] Frequently Asked Questions, Union Product Database – Q&As for industry users, Version 1.2 – February 2022 (URL: https://www.ema.europa.eu/en/documents/other/union-product-database-faqs-questions-answers-industry-users_en.pdf, accessed 12 June 2022)

[18] Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council (URL: http://data.europa.eu/eli/reg_impl/2021/17/oj, accessed 12 June 2022)

ANNEXES

Annex I : Comparison of structure and content of the DDPS and the PSMF

Annex II : QPPV oversight

Annex III: Survey – form

Annex IV: Survey – results

ANNEX I: COMPARISON OF STRUCTURE AND CONTENT OF THE DDPS AND THE PSMF

Notes: The italicized texts in the table below are quotes from the guidance and legislation mentioned in the first row of each column. The items highlighted on blue are new and do not find any corresponding items in the DDPS.

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
Not applicable	***Section A*** *containing general information regarding the pharmacovigilance system master file* – *(i) pharmacovigilance system master file reference number* – *(ii) pharmacovigilance system master file location for the purpose of pharmacovigilance inspections in accordance with Article 126(4) of Regulation (EU) 2019/6;* ***Annex I = Logbook***
a) QPPV – *The name of the QPPV located in the EEA. The business*	***Section B*** *containing information regarding the qualified person responsible for pharmacovigilance, assistant veterinary surgeon and*

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
address and contact details should be provided in the MAA form. Companies might, for example, use a 24-hour telephone number through which the QPPV or their back-up can be reached, diverting it to the appropriate person according to availability. – *A summary Curriculum Vitae (CV) of the QPPV with the key information relevant to their role (main qualifications, training and experience).* – *A summary of responsibilities* – *A description of the back-up procedure to apply in the absence of the QPPV.*	*associated back-up procedures:* – *(i) information on the qualified person responsible for pharmacovigilance including name, contact details and a signed statement from the marketing authorisation holder and the qualified person confirming that the qualified person concerned has the necessary means to fulfill the tasks and responsibilities required by Regulation (EU) 2019/6;* – *(ii) documentation on the marketing authorisation holder arrangements concerning the assistant veterinary surgeon referred to in Article 3(2), if applicable, including the contact details* – *(iii) a description of back-up arrangements that apply in the absence of the qualified person responsible for pharmacovigilance or the veterinary surgeon, assisting the qualified person responsible for pharmacovigilance referred to in Article 2(6)* ***Annex II**: additional information regarding the qualified person responsible for pharmacovigilance, assistant veterinary surgeon, and associated back-up arrangements:*

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
	– *(i) curriculum vitae including information on qualifications and training of the qualified person responsible for pharmacovigilance as referred to in Article 3(1) and, if applicable, the assistant veterinary surgeon as referred to in Article 3(2)* – *(ii) a description of the tasks and responsibilities of the qualified person responsible for pharmacovigilance* – *(iii) proof of registration with the pharmacovigilance database* – *(iv) a list of the pharmacovigilance activities that have been delegated by the qualified person responsible for pharmacovigilance to third parties*
b) Organization – *Identification and location of the company units or other organizations where the principal EEA and global pharmacovigilance activities are undertaken (in particular those sites where the main databases are located, where adverse events are collated and reported and where PSURs are prepared and processed for reporting to the competent authorities). Identification of affiliates may be made in a*	***Section C*** *containing information on the marketing authorisation holder:* – *(i) a detailed description of the organisational structure of the marketing authorisation holder, including a parent company or group of companies associated* – *(ii) the position of the qualified person responsible for pharmacovigilance within the organisation*

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
general sense, rather than affiliate-by-affiliate. – *Identification of the point(s) in the EEA at which pharmacovigilance data are accessible (to include access to adverse events, PSURs and the global pharmacovigilance data).* – *High level organization chart(s) providing an overview of the global and EEA pharmacovigilance units and organisations (identified above) and, illustrating the relationships between them, with affiliate/parent companies, and contractors. The chart(s) should show the main reporting relationships with management and clearly show the position of the EEA QPPV within the organisation. Individual names of people should not be included here. Licensing partnerships are usually product specific and should be indicated in a product specific addendum, in the MAA for that product, unless a partnership is a consistent feature of the company's organisation, across most products.* – *A brief summary of the pharmacovigilance activities undertaken by each of the organisations/units identified above.*	***Annex III**: additional information on the marketing authorisation holder:* – *(i) a list of all veterinary medicinal products covered by the pharmacovigilance system master file, including the international non-proprietary name (INN) of the active substances, if applicable, the Member States in which the product is authorised or registered, the type of procedure for authorisation and the authorisation numbers in each Member State where the product is authorised* – *(ii) a list of reference numbers for other pharmacovigilance system master files held by the same marketing authorisation holder, where applicable* – *(iii) a list of local or regional representatives for the purpose of receiving reports of suspected adverse events, including their contact details, responsibilities and territories, where applicable* – *(iv) a list of the sites where pharmacovigilance activities listed in Article 4(3), (4), (5) and (6) are carried out*

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
– *Flow diagrams indicating the flow of safety reports of different sources and types. These should indicate how reports/information are processed and reported from the source, to the point of receipt by the competent authorities. These should be limited to the major processes.*	
d) Databases – *A listing of the main databases used for pharmacovigilance purposes (e.g. compilation of safety reports, expedited/electronic reporting, signal detection, sharing and accessing global safety information) and brief functional descriptions of these should be provided including a statement regarding the validation status of the database systems.* – *A statement should be included regarding the compliance of the systems with the internationally agreed standards for electronic submission of adverse reaction reports as referred to in Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU* – *A copy of the registration, of the QPPV, with the*	***Section D** containing a description of the document management system referred to in Article 5, including the record management system for adverse event recording referred to in Article 10* No corresponding annex

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
EudraVigilance Veterinary system and identification of the process used for electronic reporting to the NCAs and the Agency. *There should be an indication of the responsibility for the operation of the databases and their location (with reference to the locations identified above under subheading "Organisation").* *g) Documentation* *Provide a brief description of the locations of the different types of pharmacovigilance source documents, including archiving arrangements. Reference can be made to the organisation charts provided above under subheading "Organisation".Section D containing a description of the document management system referred to in Article 5, including the record management system for adverse event recording referred to in Article 10*	
c) Procedures in place, which are documented in writing *An essential element of any pharmacovigilance system is that there are clear, written procedures in place. The follow procedures. The DDPS should indicate for which of these topics there are written*	***Section E** containing a description of the quality management system for pharmacovigilance activities* – *(i) a description of the processes used for pharmacovigilance activities referred to in Article 4(3), (4), (5) and (6) (see end of*

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
procedures in *place, but should not list the procedure titles per se. A procedure may cover one or more of the topics or one topic may have one or more procedures depending on its complexity and the organisation of the company. Care should be taken to ensure that quality control and review are appropriately addressed in the various processes, and reflected in the relevant procedures.* *[list of procedures]* *The DDPS should indicate the processes for which written procedures are available. A list and copies of the global and EEA procedures should be available within two working days after receipt by the MAH of competent authorities' request. Any additional local procedures should be available to respond to specific requests.* *h) Quality management system* *[…] A brief description of the responsibilities for quality assurance auditing of the pharmacovigilance system, including where appropriate auditing of sub-contractors, should be provided.*	*table for the details);* – *(ii) a description of the training management system in place referred to in Article 6(2);* – *(iii) a description of the system used for documenting or archiving information referred to in Article 5(2);* – *(iv) a description of the system for monitoring the performance of the pharmacovigilance system as referred to in Article 7* – *(v) a description of the responsibilities for quality assurance auditing of the pharmacovigilance system as referred to in Article 8 including, where appropriate, auditing of subcontractors;* – *(vi) a list of audits associated with unresolved critical or major findings;* – *(vii) a description of the corrective and preventive action plan management and change management in place as referred to in Article 9* ***Annex IV**: further details about the quality management system:*

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
f) Training *Staff should be appropriately trained for performing pharmacovigilance related activities, taking into account their role within the company. This includes not only staff within the pharmacovigilance units but also staff who may receive or process safety reports, such as sales personnel, or field trial/clinical research staff. Provide a brief description of the training system and indicate where the training records, CVs and job descriptions are filed.* *i) Supporting documentation* *The MAH should ensure that the pharmacovigilance system is in place and documented.* *An essential feature of a pharmacovigilance system is that it is clearly documented to ensure that the system functions properly, that the roles and responsibilities and required tasks are clear to all parties involved and that there is provision for proper control and when needed change of the system.*	– *(i) a list of documents, policies, procedures and processes used for the pharmacovigilance activities referred to in Article 4(3), (4), (5) and (6)* – *(ii) a list of all scheduled and completed audits including outstanding critical and major findings* – *(iii) a list of performance indicators and how to use them, as referred to in Article 7, as applicable* – *(iv) the information on training plans and records referred to in Article 6(2)* – *(v) the methodology to calculate the factor referred to in Article 14(2);* – *(vi)a list of risk management measures and the outcome of risk minimisation measures;*
e) Contractual arrangements with other persons or organizations involved in the fulfillment of pharmacovigilance obligations	***Section F** containing a description of the contractual arrangements between marketing authorisation holders and third parties concerning*

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
Links with other organisations such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. The company should identify the major subcontracting arrangements it has for the conduct of its pharmacovigilance activities and the main organisations to which it has subcontracted these (in particular where the role of the QPPV, the electronic reporting of adverse events, the main databases, signal detection, or the compilation of PSURs is subcontracted). *A brief description of the nature of the agreements the company establishes with co-marketing partners and contractors for pharmacovigilance activities should be provided. Co-licensing or co-marketing arrangements within the EEA should be identified and the distribution of the major responsibilities between the parties made clear.* *Since co-licensing or co-marketing arrangements are mainly product specific, any information on these may be provided in a product specific addendum, in the MAA. Likewise if subcontracting is product specific this should be indicated in a product specific addendum.*	*pharmacovigilance activities, where applicable.* ***Annex V**: further information on contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities:* – *(i) a list of the activities or services subcontracted by the marketing authorisation holder to third parties to fulfil pharmacovigilance obligations and information on who the activities or services are subcontracted to, including the name and address any subcontractors, where applicable;* – *(ii) a list of the tasks of the qualified person responsible for pharmacovigilance referred to in Article 78 of Regulation (EU) 2019/6 that have been totally or partially outsourced and the information on who the activities or services are subcontracted to, including the name and address of the subcontractor(s), where applicable;* – *(iii) a list of existing contracts and agreements with third parties, where applicable, including the products and territories concerned.*

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
List of procedures as per part c) – *The activities of the QPPV and the back-up procedure to apply in their absence.* – *The collection, processing (including data entry and data management), quality control, coding, classification, veterinary review and reporting of adverse events:* – *Reports of different types: Organised data collection schemes (solicited), unsolicited, clinical trials, literature* – *The process should ensure that reports from different sources are captured:* – *EEA and third countries, veterinarians and other health care professionals, animal owners, sales and marketing personnel, and other MAH personnel, licensing partners, competent authorities, others* – *The follow-up of reports for missing information and for information on the progress andoutcome of the case(s)* – *Detection of duplicate reports* – *Expedited reporting*	Details on the processes used for pharmacovigilance activities and refered to in section E and annex IV.1: • *Art 4(3): document management, training, audit and change management* • *Art 4(4):* – *(a) initial recording of any suspected adverse event;* – *(b) collection of additional data;* – *(c) collation of reports of suspected adverse events and additional data;* – *(d) data handling other than mentioned in points (a) to (c);* – *(e) evaluation of data;* – *(f) monitoring of quality, integrity and completeness of all information registered in the pharmacovigilance system including information reported to the Union pharmacovigilance database and management of duplicates;* – *(g) recording of any adverse event in the Union pharmacovigilance database;*

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
– *Electronic reporting* – *PSURs: The preparation, processing, quality control, review including veterinary review and reporting* – *Global pharmacovigilance activities applying to all products: Continuous safety profile of authorised VMPs (product-specific risk management and pharmacovigilance planning are not addressed in this Chapter):* – *Signal detection and review,* – *Benefit-risk assessment,* – *Reporting and communication notifying CA and health care professionals of changes to the risk-benefit balance of products, etc* – *Interaction between safety issues and product defects* – *Responses to requests for information from competent authorities* – *Handling of urgent safety restrictions and safety variations* – *Meeting commitments to competent authorities in relation to a marketing authorisations*	– *(h) archiving of all relevant documents.* • *Art 4(5): risk management, monitoring of the benefit-risk balance, signal management and communication to all relevant staekholders* • *Art 4(6): maintenance and availability of the PSMF*

DDPS: sections and content Volume 9 B – Part I, section 2.3.3	**PSMF: sections and content** IR 2021/1281
– *Management and use of databases or other recording systems* – *Internal audit of the pharmacovigilance system* – *Training* – *Archiving*	

ANNEX II : OVERSIGHT OF THE QPPV

Items the QPPV shall have oversight on	Corresponding PSMF sections and annexes
Applicable legislation: • Reg 2019/6, Art. 78 • VGVP on PSMF, section 2.1 Note: the items have been grouped when information can be found in one and the same section of the PSMF or the same annex.	Applicable legislation. • IR (EU) 2021/1281, Art.. 22 and following
Quality control and assurance procedures Standard operating procedures	Section E containing a description of the quality management system for pharmacovigilance activities – (i) a description of the processes used for pharmacovigilance activities referred to in Article 4(3), (4), (5) and (6) (see end of table for the details); – (iii) a description of the system used for documenting or archiving information referred to in Article 5(2); Annex IV: further details about the quality management system:

Items the QPPV shall have oversight on	Corresponding PSMF sections and annexes
	– (i) a list of documents, policies, procedures and processes used for the pharmacovigilance activities referred to in Article 4(3), (4), (5) and (6)
PSMF preparation and maintenance	Section A containing general information regarding the pharmacovigilance system master file Annex I: Logbook if changes in PSMF main part Section E containing a description of the quality management system for pharmacovigilance activities – (i) a description of the processes used for pharmacovigilance activities referred to in Article 4(3), (4), (5) and (6) (see end of table for the details); – (iii) a description of the system used for documenting or archiving information referred to in Article 5(2); Annex IV: further details about the quality management system: – (i) a list of documents, policies, procedures and processes used for the pharmacovigilance activities referred to in Article 4(3), (4), (5) and (6)

Items the QPPV shall have oversight on	Corresponding PSMF sections and annexes
Database operations	Section D containing a description of the document management system referred to in Article 5, including the record management system for adverse event recording referred to in Article 10 Annex I: logbook if changes in the PV database used
Safety reporting, signal management	Section C containing information on the marketing authorisation holder: – (i) a detailed description of the organisational structure of the marketing authorisation holder, including a parent company or group of companies associated – (ii) the position of the qualified person responsible for pharmacovigilance within the organisation Annex III: additional information on the marketing authorisation holder: – (i) a list of all veterinary medicinal products covered by the pharmacovigilance system master file, including the international non-proprietary name (INN) of the active substances, if applicable, the Member States in which the product is authorised or registered, the type of procedure

Items the QPPV shall have oversight on	Corresponding PSMF sections and annexes
	for authorisation and the authorisation numbers in each Member State where the product is authorised – (ii) a list of reference numbers for other pharmacovigilance system master files held by the same marketing authorisation holder, where applicable – (iii) a list of local or regional representatives for the purpose of receiving reports of suspected adverse events, including their contact details, responsibilities and territories, where applicable – (iv) a list of the sites where pharmacovigilance activities listed in Article 4(3), (4), (5) and (6) are carried out Annex IV: – (vi) a list of risk management measures and the outcome of risk minimisation measures
Post-marketing surveillance studies	No corresponding section nor annex
Communication to stakeholders	No corresponding section nor annex
Contractual/sub-contractual arrangements	Section F containing a description of the contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities, where

Items the QPPV shall have oversight on	Corresponding PSMF sections and annexes
	applicable. Annex V: further information on contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities: – (i) a list of the activities or services subcontracted by the marketing authorisation holder to third parties to fulfill pharmacovigilance obligations and information on who the activities or services are subcontracted to, including the name and address any subcontractors, where applicable; – (ii) a list of the tasks of the qualified person responsible for pharmacovigilance referred to in Article 78 of Regulation (EU) 2019/6 that have been totally or partially outsourced and the information on who the activities or services are subcontracted to, including the name and address of the subcontractor(s), where applicable; – (iii) a list of existing contracts and agreements with third parties, where applicable, including the products and territories concerned.
Compliance data (e.g. in relation to the quality, completeness and timelines for safety reporting and signal management)	Section E containing a description of the quality management system for pharmacovigilance activities:

Items the QPPV shall have oversight on	Corresponding PSMF sections and annexes
	– (iv) a description of the system for monitoring the performance of the pharmacovigilance system as referred to in Article 7 Annex IV: – (iii) a list of performance indicators and how to use them, as referred to in Article 7, as applicable
Audit reports; Preventive or corrective action plan preparation and implementation	Section E containing a description of the quality management system for pharmacovigilance activities: – (v) a description of the responsibilities for quality assurance auditing of the pharmacovigilance system as referred to in Article 8 including, where appropriate, auditing of subcontractors; – (vi) a list of audits associated with unresolved critical or major findings; – (vii) a description of the corrective and preventive action plan management and change management in place as referred to in Article 9 Annex I: logbook for update to section E on list of audits associated with unresolved critical and major findings

Items the QPPV shall have oversight on	Corresponding PSMF sections and annexes
	Annex IV: – (ii) a list of all scheduled and completed audits including outstanding critical and major findings
Training of personnel in relation to pharmacovigilance	Section E containing a description of the quality management system for pharmacovigilance activities: – (ii) a description of the training management system in place referred to in Article 6(2); Annex IV: – (iv) the information on training plans and records referred to in Article 6(2)

ANNEX III: SURVEY – FORMS

EU Regulation 2019/6 – Survey to introduction of the PSMF

Dear members of the Pharmacovigilance Working Group, dear colleagues,

in the scope of a Master for Drug Regulatory Affairs I'm enrolled at the university of Bonn, I'm conducting a survey related to the new Pharmacovigilance System Master File. With the Veterinary Regulation 20219/6 and its Implementing Regulation 2021/1281, the Detailed Description of the Pharmacovigilance System (DDPS) will be replaced by the PSMF. I'm exploring the switch from the DDPS to the PSMF and its impact of the PV department in vet companies.

You plan to introduce a PSMF in your company. Thank you very much for accepting to share your views on the introduction of this document in your company and the challenges you encountered. The survey should not take more than 10 minutes of your time.

With best regards
Magali Quetin
Head of EU GPV
Boehringer-Ingelheim Vetmedica GmbH

EU Regulation 2019/6 - Survey to introduction of the PSMF

Implementation strategy

A. Your first version of the PSMF...

- ○ will be fully ready by 28 January 2022
- ○ will be drafted by 28 January 2022
- ○ will be drafted at some time point within 2022

B. In your company, you will introduce...

- ○ one single PSMF
- ○ several PSMFs:
  - ○ one per DDPS you have
  - ○ because you take the opportunity to re-organize your PV system

Creation of the main part (sections A to F)

C. How many text from the previous DDPS do you estimate you'll be able to reuse to create the main part (sections A to F) of the PSMF?

- ○ 50 %
- ○ 80%
- ○ more than 80%

D. Would you say the description of your PV system in the PSMF's main part (sections A to F) is more detailed or less detailed than in the previous DDPS?

- ○ more details
- ○ less details

E. And why? (several choices possible)

- ☐ because you adapt the level of details to the requirements of the Implementing Regulation 2021/1281
- ☐ because the main part should remain quite constant and not impacted by any operative changes in your PV system
- ☐ because you're awaiting for lessons learned from the first inspections to adapt the level of details to the authorities expectations

EU Regulation 2019/6 – Survey to introduction of the PSMF

Creation of the annexes

F. Which 3 annexes are the most challenging to create within your company? Please choose 3 and rank them by 1, 2 and 3.

- ☐ Annex I: a logbook
- ☐ Annex II: additional information regarding the qualified person responsible for pharmacovigilance,
- ☐ Annex III[1] (i) a list of all veterinary medicinal products covered by the pharmacovigilance system master file
- ☐ Annex III (ii) a list of reference numbers for other pharmacovigilance system master files held by the same marketing authorisation holder, where applicable;
- ☐ Annex III (iii) a list of local or regional representatives
- ☐ Annex III (iv) a list of the sites where pharmacovigilance activities listed in Article 4(3), (4), (5) and (6) are carried out;
- ☐ Annex IV[2] (i) a list of documents, policies, procedures and processes used for the pharmacovigilance activities
- ☐ Annex IV (ii) a list of all scheduled and completed audits including outstanding critical and major findings.;
- ☐ Annex IV (iii) a list of performance indicators and how to use them
- ☐ Annex IV (iv) the information on training plans and records;
- ☐ Annex IV (v) the methodology to calculate the factor referred to in Article 14(2);
- ☐ Annex IV (vi) a list of risk management measures and the outcome of risk minimisation measures;
- ☐ Annex V[3] (i) a list of the activities or services subcontracted by the marketing authorisation holder to third parties
- ☐ Annex V (ii) a list of the tasks of the qualified person responsible for pharmacovigilance that have been totally or partially outsourced
- ☐ Annex V (iii) a list of existing contracts and agreements with third parties

What is for each for the 3 the challenges encountered? (several choices possible)

For 1:

- ☐ Information not available at one single point within the company yet
- ☐ Level of details required not available at one single point within the company yet
- ☐ Tracking and electronic systems in use to store the information required are not designed to deliver it (i.e. no or limited reporting functionalities)
- ☐ Lack of cooperation from interacting departments and/or data owners with PV
- ☐ Lack of guidance from the authorities or delay in guidance publication
- ☐ Other, please specify

For 2:

- ☐ Information not available at one single point within the company yet
- ☐ Level of details required not available at one single point within the company yet
- ☐ Tracking and electronic systems in use to store the information required are not designed to deliver it (i.e. no or limited reporting functionalities)
- ☐ Lack of cooperation from interacting departments and/or data owners with PV
- ☐ Lack of guidance from the authorities or delay in guidance publication
- ☐ Other, please specify

[1] Annex III: additional information on the marketing authorisation holder

[2] Annex IV: further details about the quality management system

[3] Annex V: further information on contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities

For 3:

- ☐ Information not available at one single point within the company yet
- ☐ Level of details required not available at one single point within the company yet
- ☐ Tracking and electronic systems in use to store the information required are not designed to deliver it (i.e. no or limited reporting functionalities)
- ☐ Lack of cooperation from interacting departments and/or data owners with PV
- ☐ Lack of guidance from the authorities or delay in guidance publication
- ☐ Other, please specify

G. Do you see these challenges encountered have an impact for the first version of your company's PSMF:

- ○ Yes
- ○ No

If yes, please specify (several choices possible)

- ☐ You consider the document potentially incomplete.
- ☐ You consider the quality of the document not at the appropriate level yet.
- ☐ The data may be not reliable

H. What is your strategy during 2022 for the annexes of your company's PSMF?

- ○ Update on regular basis.

  If you tick this choice, please specify the update interval envisaged:

  - ○ monthly
  - ○ quarterly
  - ○ 6-monthly
- ○ Update after more guidance and first lessons learned from PV inspections are available
- ○ No update in 2022

Maintenance process of the PSMF

I. For the maintenance of the annexes...

- ○ you will develop a process for each annex, as you create them.
- ○ you will develop the process during 2022, after the first version of each annex is available.

J. Logbook: how do you plan to detect changes to the information included in the annexes that would have an impact of the main part and therefore would require inclusion into the logbook?

- ☐ Manual process of review and comparison of the annexes content
- ☐ Semi-automated process
- ☐ You expect the data owner to provide an overview of the changes in comparison to the previous version.

K. Resources for the future maintenance process: how do you estimate the resource needs for the maintenance of the PSMF in your company?

- ○ One dedicated FTE
- ○ 0.5 dedicated FTE
- ○ Less than 0.5 dedicated FTE

L. Do you plan to externalize/outsource the maintenance of your company's PSMF?

- ○ Yes
- ○ No

Filing/archiving and publishing

M. Do you plan to use a dedicated tool to manage the filing/archiving of the single parts (main part, annexes) of your PSMF?

- ○ Yes.
- ○ No

If yes, what is/are the reason(s) (multiple choices possible)?

- ☐ Compliance with the regulatory requirements.
- ☐ The tool is already available in your company
- ☐ Efficiency of the maintenance process.

N. In case of request by the authorities, the PSMF should be compiled and sent within 7 days. How do you intent to compile the document together?

- ○ Manually
- ○ Using a publishing tool

Your company is…

- ○ an SME
- ○ a large company

Your company has affiliates…

- ○ all over the world
- ○ in EU only

The QPPV function has been outsourced by your company:

- ○ Yes
- ○ No

Thank you very much for your participation! Please send the form back to Magali.quetin@boehringer-ingelheim.com

New Veterinary Regulation (EU) 2019/6 – Survey to introduction of the PSMF

Dear members of the Pharmacovigilance Working Group, dear colleagues,

I’m writing to you as a private person, this is not an initiative from my company Boehringer-Ingelheim. In the scope of a Master for Drug Regulatory Affairs I'm enrolled at the university of Bonn, I'm conducting a survey related to the new Pharmacovigilance System Master File. With the New Veterinary Regulation (EU) 2019/6 and its Implementing Regulation (EU) 2021/1281, the Detailed Description of the Pharmacovigilance System (DDPS) has been replaced by the PSMF. I'm exploring the switch from the DDPS to the PSMF and its impact of the PV department in vet companies.

You have introduced or plan to introduce the PSMF in your company. Thank you very much for accepting to share your views on the introduction of this document in your company and the challenges you encountered. The survey should not take more than 10 minutes of your time.

With best regards
Magali Quetin
Head of EU GPV
Boehringer-Ingelheim Vetmedica GmbH

Implementation strategy

A. Your first version of the PSMF...

- ○ was fully ready by 28 January 2022
- ○ was drafted by 28 January 2022
- ○ will be drafted/ready at some time point within 2022

B. In your company, you introduced/will introduce...

- ○ one single PSMF
- ○ several PSMFs:
  - ○ one per DDPS you have
  - ○ because you take the opportunity to re-organize your PV system

Creation of the main part (sections A to F)

C. How many text from the previous DDPS do you estimate you was able to reuse to create the main part (sections A to F) of the PSMF?

- ○ 50 %
- ○ 80%
- ○ more than 80%

D. Would you say the description of your PV system in the PSMF's main part (sections A to F) is more detailed or less detailed than in the previous DDPS?

- ○ more details
- ○ less details

E. And why? (several choices possible)

- ☐ because you adapt the level of details to the requirements of the Implementing Regulation 2021/1281
- ☐ because the main part should remain quite constant and not impacted by any operative changes in your PV system
- ☐ because you're awaiting for lessons learned from the first inspections to adapt the level of details to the authorities expectations

Creation of the annexes

F. Which 3 annexes are the most challenging to create within your company? Please choose 3 and rank them by 1, 2 and 3.

- ☐ Annex I: a logbook
- ☐ Annex II: additional information regarding the qualified person responsible for pharmacovigilance,
- ☐ Annex III[1] (i) a list of all veterinary medicinal products covered by the pharmacovigilance system master file
- ☐ Annex III (ii) a list of reference numbers for other pharmacovigilance system master files held by the same marketing authorisation holder, where applicable;
- ☐ Annex III (iii) a list of local or regional representatives
- ☐ Annex III (iv) a list of the sites where pharmacovigilance activities listed in Article 4(3), (4), (5) and (6) are carried out;
- ☐ Annex IV[2] (i) a list of documents, policies, procedures and processes used for the pharmacovigilance activities
- ☐ Annex IV (ii) a list of all scheduled and completed audits including outstanding critical and major findings.;
- ☐ Annex IV (iii) a list of performance indicators and how to use them
- ☐ Annex IV (iv) the information on training plans and records;
- ☐ Annex IV (v) the methodology to calculate the factor referred to in Article 14(2);
- ☐ Annex IV (vi) a list of risk management measures and the outcome of risk minimisation measures;
- ☐ Annex V[3] (i) a list of the activities or services subcontracted by the marketing authorisation holder to third parties
- ☐ Annex V (ii) a list of the tasks of the qualified person responsible for pharmacovigilance that have been totally or partially outsourced
- ☐ Annex V (iii) a list of existing contracts and agreements with third parties

What is for each for the 3 the challenges encountered? (several choices possible)

For 1:

- ☐ Information not available at one single point within the company yet
- ☐ Level of details required not available at one single point within the company yet
- ☐ Tracking and electronic systems in use to store the information required are not designed to deliver it (i.e. no or limited reporting functionalities)
- ☐ Lack of cooperation from interacting departments and/or data owners with PV
- ☐ Lack of guidance from the authorities or delay in guidance publication
- ☐ Other, please specify

For 2:

- ☐ Information not available at one single point within the company yet
- ☐ Level of details required not available at one single point within the company yet
- ☐ Tracking and electronic systems in use to store the information required are not designed to deliver it (i.e. no or limited reporting functionalities)
- ☐ Lack of cooperation from interacting departments and/or data owners with PV
- ☐ Lack of guidance from the authorities or delay in guidance publication
- ☐ Other, please specify

[1] Annex III: additional information on the marketing authorisation holder

[2] Annex IV: further details about the quality management system

[3] Annex V: further information on contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities

For 3:

- ☐ Information not available at one single point within the company yet
- ☐ Level of details required not available at one single point within the company yet
- ☐ Tracking and electronic systems in use to store the information required are not designed to deliver it (i.e. no or limited reporting functionalities)
- ☐ Lack of cooperation from interacting departments and/or data owners with PV
- ☐ Lack of guidance from the authorities or delay in guidance publication
- ☐ Other, please specify

G. Do you see these challenges encountered have an impact for the first version of your company's PSMF:

- ◉ Yes
- ○ No

If yes, please specify (several choices possible)

- ☐ You consider the document potentially incomplete.
- ☐ You consider the quality of the document not at the appropriate level yet.
- ☐ The data may be not reliable

H. What is your strategy during 2022 for the annexes of your company's PSMF?

- ○ Update on regular basis.

If you tick this choice, please specify the update interval envisaged:

- ○ monthly
- ○ quarterly
- ○ 6-monthly

- ○ Update after more guidance and first lessons learned from PV inspections are available
- ○ No update in 2022

Maintenance process of the PSMF

I. For the maintenance of the annexes...

- ○ you developed a process for each annex, as you created them.
- ○ you will develop the process during 2022, after the first version of each annex is available.

J. Logbook: how do you plan to detect changes to the information included in the annexes that would have an impact of the main part and therefore would require inclusion into the logbook?

- ☐ Manual process of review and comparison of the annexes content
- ☐ Semi-automated process
- ☐ You expect the data owner to provide an overview of the changes in comparison to the previous version.

K. Resources for the future maintenance process: how do you estimate the resource needs for the maintenance of the PSMF in your company?

- ○ One dedicated FTE
- ○ 0.5 dedicated FTE
- ○ Less than 0.5 dedicated FTE

L. Do you plan to externalize/outsource the maintenance of your company's PSMF?

- ○ Yes
- ○ No

Filing/archiving and publishing

M. Do you plan to use a dedicated tool to manage the filing/archiving of the single parts (main part, annexes) of your PSMF?

- ○ Yes.
- ○ No

If yes, what is/are the reason(s) (multiple choices possible)?

- ☐ Compliance with the regulatory requirements.
- ☐ The tool is already available in your company
- ☐ Efficiency of the maintenance process.

N. In case of request by the authorities, the PSMF should be compiled and sent within 7 days. How do you intent to compile the document together?

- ○ Manually
- ○ Using a publishing tool

Your company is…

- ○ an SME
- ○ a large company

Your company has affiliates…

- ○ all over the world
- ○ in EU only

The QPPV function has been outsourced by your company:

- ○ Yes
- ○ No

Thank you very much for your participation! Please send the form back to Magali.quetin@boehringer-ingelheim.com

ANNEX IV: SURVEY – RESULTS

question number	A	B		C	D	E	F. An		
company	first version of PSMF available at	introduction of a single PSMF?	reason for introduction several PSMFs	reused part from DDPS?	detail level?	why?	challenge 1	reason(s)	challenge 2
1	28.01.22	yes	na	0.8	more	adapt to IR	LPV	interacting dpt	SDEA
2	28.01.22	yes	na	0.5	less	all choices	SDEA	E-system	activities outs
3	28.01.22	no	one PSMF per DDPS	0.5	more	adapt to IR	SOP	E-system, allocation of doc shared with HP	training
4	28.01.22	yes	na	0.5	less	main part constant, lessons learned	SDEA	single point, e-system, missing guidance	risk minimization measures
5	28.01.22	yes	na	0.8	not answered	adapt to IR	SDEA	E-system, single point and details	logbook
6	28.01.22	yes	na	0.5	more	adapt to IR, main part constant	SDEA	single point, details, e-system , interacting dpt	dose factor
7	draft	yes	na	0.8	more	adap to IR	MA	interacting dpt	SOP
8	draft	yes	na	0.5	more	adapt to IR	KPI	e-system, update with each PSMF version	dose factor

question number	nexes			G		H	I	J	K
company	reason(s)	challenge 3	reason(s)	impact of those challenges on the first version?	which one(s)?	update in 2022?	maintenance process for annexes	maintenance of logbook	FTE dedicated to PSMF
1	interacting dpt	MA	E-system	yes	reliable	6-monthly	creation process ongoing	manual	<0.5
2	guidance EMA	MA	E-system	no		wait for guidance	creation process ongoing	Semi-automated	<0.5
3	not at one point	audit	no specific audit or inspection yet	no		wait for guidance	creation process ongoing	manual	<0.5
4	single point and with details, missing guidance	audit	E-system, guidance	yes	all	quarterly	after first version created	manual, data owner	<0.5
5	automated system that will automatically build up the logbook			yes	quality	quarterly	creation process ongoing	automated in future	<0.5
6	single point, details, e-system , interacting dpt	audit	details, e-system , interacting dpt	yes	all	wait for guidance	creation process ongoing	Semi-automated	<0.5
7	none	LPV	single point	yes		no	creation process ongoing	data owner	1
8	guidance EMA	SOP	E-system	no		6-monthly	creation process ongoing	manual	<0.5

question number	L	M	N	general information		
company	outsourcing of the PSMF	use of dedicated PSMF tool	compilation method	size of the company	affiliates	role of QPPV outsourced?
1	no	yes, available, compliance	manual	SME	EU	no
2	no	yes, available, efficiency	manual	large	www	no
3	no	no	manual	large	www	no
4	no	yes, cmpliance, efficiency	manual	large	www	no
5	no	yes, no reasc	publishing	large	www	no
6	no	yes, available, efficiency, complaince	manual	large	www	no
7	no	no	manual	SME	EU	no
8	no	yes, available, efficiency, complaince	publishing	large	EU	no

ERKLÄRUNG

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

Ort, Datum des Abgabetermins

_____

Unterschrift

_____