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Position paper

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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)

Background

Articles 76, 77, 78 and 81 of the veterinary legislation EU Regulation 2019/6 define the responsibilities of the Marketing Authorisation Holder (MAH) in pharmacovigilance activities. In particular, article 77(2), requires that MAHs shall have in place one or more Pharmacovigilance System Master Files (PSMF) describing in detail the pharmacovigilance (PhV) system with respect to its authorised veterinary medicinal products (VMPs) in the EU/EEA. For each VMP, the MAH shall not have more than one pharmacovigilance system master file. And article 81, requires MAHs to carry out a signal management process for their VMPs.

Article 77(6) of EU Regulation 2019/6 requires the Commission to adopt an implementing regulation on good pharmacovigilance practice and also on the format and content of the pharmacovigilance system master file and its summary.

1. General considerations

A general concern relates to the practical implementation of some of the requirements laid down in this Implementing Act. Some of the requirements will increase the administrative burden, if not implemented correctly with appropriate tools available (e.g., UPD and UPhVD set up). In particular, MAHs shall ensure that adverse event reports, concerning their VMPs reported to the UPhVD from other sources, are recorded in their own database. Therefore, the Agency must ensure that tools are available to enable search and download of cases from the EU database into the MAH's system. Consequently, it will be critical for achieving a primary objective of the review of the legislation, to reduce administrative burden for all parties, that these databases and the processes needed to populate and maintain them, are established with this objective always in sharp focus.

Part of this Implementing Act's content applies specifically to MAHs. However, other parts of this Implementing Act should apply to MAHs and regulatory authorities and the Agency. It would therefore be beneficial if a general note to this effect would be included.

It is highly recommended to add a glossary of terms to provide a clear definition of standard terms that are present throughout the document and would merit clarification. Some definitions are missing in this document, for instance for some more high-level concepts such as post-marketing study, risk management system and risk management. Finally, we would encourage the Commission to use consistent definitions of terms between the different documents, e.g. for "signal", the CIOMS definition should apply.

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Important to note is that implementation of these regulations will require significant effort and resources in organisations to adapt the current systems and procedures. Much of the guidance are only drafts at this time and we fear that the time to approval will not leave adequate time to update systems, processes and procedures as per existing Quality Management Systems. **Therefore, the implementing act should include an implementation period**, starting after the implementing act is published, to facilitate the transition and adoption of these new regulations. Transition periods have a precedent in Human Pharmacovigilance; the same should apply here.

2. Main concerns

2.1 Article 14: Provision of additional data

"*1. To enable comprehensive analysis of adverse event reports from third countries, marketing authorisation holders shall record in the Union product database the corresponding product names and authorisation numbers for the same product or, if the same product is not authorised in the Union, for a similar product authorised in the Union, as defined in the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Guideline 24. Marketing authorisation holders shall update the information when necessary.*"

AnimalhealthEurope does not consider that this level of detail should be included in the IA at this time and strongly recommend that this item is amended. The reason for this is while MAH fully understand and accept the requirement for this or a similar functionality, this topic has not yet been discussed in any detail (it is therefore not sure that this is the best solution which is going to be available for 2022 or even in 2027 or 2032). This is a problem which many international agencies face and it is likely that a harmonised approach (which the current proposal is not) will be proposed / implemented over the timeline of this Act. For this reason, a more flexible / high level wording is recommended. AnimalhealthEurope would like to suggest an alternative approach such as the text below (note - while the 'means' is recommended to be managed by guidance, the requirement for MAH to update the information would remain in the legal text):

> "*To enable comprehensive analysis of adverse event reports from third countries, **the Agency shall publish guidance as to how marketing authorisation holders shall inform the Agency of** the corresponding product names and authorisation numbers for the same product or, if the same product is not authorised in the Union, for a similar product authorised in the Union (as defined in the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Guideline 24). Marketing authorisation holders shall update the information **as required.**"*

2.2 Article 14: Incidence calculation

"2. To calculate the estimated number of animals treated from the information on volume ofsales required under Article 58(12) of Regulation (EU) 2019/6, marketing authorisation holders shall identify and provide a factor to the Union product database for each of their veterinary medicinal products according to country, target species and pack size."

Article 58(12) of Regulation 2019/6* does only require reporting the sales volume per veterinary medicinal product and not per pack size. It is therefore proposed to delete "**and pack size**". It is further proposed to delete "**according to country**" as the requirement is per veterinary medicinal product, which implies that it should be per country. It is our understanding that such details, especially "pack size", will be further defined in guidelines and should not be mentioned in the Implementing Act.

*Article 58(12) of Regulation 2019/6: The marketing authorisation holder shall record in the product database the annual volume of sales for each of its veterinary medicinal products.

2.3 Article 22: Content and structure of the pharmacovigilance system master file

"3. The pharmacovigilance system master file shall contain the following Annexes:
(c) 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;"

AnimalhealthEurope believes this is **unnecessary** because this information will be already available and maintained in the Union Product Database (UPD) since each product can only be linked to a single PSMF within the UPD. *Ergo* the UPD can be interrogated by the Agency / Competent Authorities or other stakeholders to identify all such products connected to a specific PSMF. For this reason, it is recommended that this requirement is removed.

However, if it is not removed, one assumes that a MAH could choose to use the UPD as the source of this list and generate a report as needed from the UPD (however, this only really confirms that this requirement is unnecessary and redundant).

2.4 Article 23: Summary (of PSMF)

It is very important to industry that the summary of the PSMF does not contain:

(c) *name, contact details and place of operation of the qualified person 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.

Reasoning

Considering that the PSMF Summary is part of all MA dossiers, changes to the information required in points (c), (d) and (e), will require variations to the PSMF Summary for all concerned products which can represent a huge administrative burden for the MAH and the authorities, as well as important costs. For example, the current experience is that the overall amount of fees can reach several hundred thousand euros for a medium-sized company. This should be avoided as these pieces of information will be available in the databases. This was one of the main issues with the DDPS, and it was one of the administrative burdens that was supposed to be resolved with the implementation of the PSMF. In particular, a change of QPPV is always possible, for personal reasons, internal promotions etc. Such a change triggering possibly hundreds of thousands of euros will limit the career development of the persons in charge or create an unfair penalty for the companies who want to promote internal mobility or need to respect individual decisions such as a geographical move.

- The purpose of the summary is to ensure that a product is indeed part of a PV system, and define the site of inspection, thus (a) the pharmacovigilance system master file reference number and (b) the pharmacovigilance system master file location; should be sufficient.
- The knowledge of the PSMF file reference number (and its location) should provide immediate link to any further information on the PSMF details including those mentioned in point c, d and e (presumably in the Union PhV database). Therefore, the absence of point c, d and e in the

summary of the PSMF does not compromise any immediate access to information on the PSMF details relating to the product.

3. Other concerns

3.1 Article 6: Training

"All personnel involved in the performance of pharmacovigilance activities shall receive initial and continuous training for their role and responsibilities in relation to the activities mentioned in Article 4, paragraphs 3 to 6, also including activities related to clinical trials, technical product complaints, standards, sales and marketing."

We do not see the rationale to train pharmacovigilance personnel on marketing or sales activities. The reference to article 4, §3 to 6 is sufficient. Please delete the second part of the sentence to read:

"All personnel involved in the performance of pharmacovigilance activities shall receive initial and continuous training for their role and responsibilities in relation to the activities mentioned in Article 4, paragraphs 3 to 6."

3.2 Article 9: Corrective and preventive action and change management

"4. Change management shall provide for a controlled process of change, including monitoring and documenting the effectiveness of the corrective or preventive actions and communication to relevant stakeholders."

The terminology 'corrective and preventative actions' is typically used in relation to deviations. As this paragraph refers to change management, AnimalhealthEurope believes the actions mentioned in this paragraph should be referred to as change actions. Please amend the text to read:

"4. Change management shall provide for a controlled process of change, including monitoring and documenting the effectiveness of the change actions and communication to relevant stakeholders."

3.3 Article 12: Recording of adverse events

"1. Information concerning suspected adverse events shall be recorded and coded using internationally agreed standards. The latest version of the standards shall be used in line with the specified implementation dates."

While AnimalhealthEurope fully agrees with the principle to always use the latest version of the standards, there are cases where a gap between the approval of the standard and publication & entry into force is observed. It is of concern that for some specific and practical circumstances, an outdated version would still be used in this short intermediate period which could be considered as a violation of this article 12(1). The text as proposed in this IA, is too rigid and does not provide sufficient room for evaluation of the practical situation. It is proposed to remove the second sentence from this IA and include the detail of these particular circumstances in the relevant guidelines (under discussion currently). Please amend the text to read:

"1. Information concerning suspected adverse events shall be recorded and coded using internationally agreed standards."

3.4 Article 13: Adverse Event Reporting

"2. A language customary in the field of medical science shall be used to record non- coded information in the Union pharmacovigilance database, including such information related to adverse events originating outside the Union."

For the smooth and efficient running of the Union Pharmacovigilance network, it is essential for the Agency, all NCAs and all MAHs that all data are immediately available in a standard format including a common language. MAHs should not be obliged to translate NCA cases submitted in National language only and there are occasions where this will likely lead to confusion (for example, if an NCA is the originator and the case involves products from 2 different MAHs, each MAH may provide their own version of translation that could be different from the original text generated by the NCA in the first place). This is also very important from a signal management perspective. It should not be a requirement for only the MAH to provide the narrative summary in the EN language – this should be applicable for NCA source reports as well. As a general rule, the case originator, regardless whether it is a MAH or NCA, should provide an EN summary (translation) in addition to their local language version (if they want to include this local language version).

3.5 Article 15: Post-marketing surveillance studies

"1. Post-marketing surveillance studies may be conducted by a marketing authorisation holder on his own initiative or on request of the Agency or a competent national authority in accordance with Article 76(3) and (4) of Regulation (EU) 2019/6."

The overarching principle of risk-based approach should always prevail. Essentially, the request for a specific post-marketing study should be triggered by the concerns that a VMP could pose from a benefit/risk perspective. The reasons to request a specific post-marketing surveillance study should be scientifically sound, harmonised between NCAs and EMA. In addition, such guidance should be published.

"6. .. the marketing authorisation holder shall provide a translation of the title, the summary of the study protocol and a summary of the final report of the study in a language customary in the field of medical science."

There is much concern that translation of information will represent additional burden. In addition, it is not clear what "the language customary in the field of medical science" is? Only English should be considered the PhV Language for EU and we strongly advocate to clarify this in the document. The "language customary in the field of medical science" should be clearly stated as being English.

3.6 Article 22: Content and structure of the pharmacovigilance system master file

3.6.1: 22(2)(e)(iii): *"a description of the system used for documenting or archiving information referred to in Article 5(2);"*

This section seems to be an effective duplicate of article 22(2)(d) which covers the requirement (documenting or archiving) in more detail. In addition, the reference to article 5(2) is incorrect, as it should be 5(1) and does not refer to any specific information. It is therefore suggested to delete section 22(2)(e)(iii).

3.6.2: 22(2)(e)(vi): *"a list of audits associated with unresolved critical or major findings;"*

This appears to be a duplicate as this information is also required by Article 8(3) on Audits, which clearly refers to Annex IV (ii) where a list of all scheduled and completed audits including outstanding critical and major findings shall be documented. It is therefore suggested to delete section 22(2)(e)(vi).

3.6.3: 22(3)(d)(vi): *"a list of risk management measures and the outcome of risk minimisation measures;"*

This seems to be a new requirement and would merit some clarification as it is not entirely clear what is intended. In addition, as written this doesn't seem to fit within the section regarding quality management systems (22(3)(d) 'Annex IV: further details about the quality management system'.

3.6.4: 22(3)(e)(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;"*

This seems to be a duplication of section 22(3)(b)(iv). It is suggested to delete section 22(3)(b)(iv).

3.7 Article 24: Maintenance

"3. The pharmacovigilance system master file shall be subject to version control and indicate the date when it was last updated."

"4. 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".

A properly managed version control would also be able to capture the information as required in paragraph 4 and could be a more efficient way of handling this. Requiring both a logbook and version control could therefore result in a duplication of tasks and an increase in the administrative burden for MAHs. Therefore, it is suggested to merge paragraphs 3 and 4 into one single paragraph. The following amended text is proposed:

"3. Marketing authorisation holders shall record in a logbook or via version control 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 document the following information: the changed Section, the kind of change, the date, the person responsible and, where appropriate, the reason for the alteration".

3.8 Article 25: Location and availability

Considering the potential volume of the PSMF, including annexes, the ability to print a copy appears to be a waste of resources and is not environmentally friendly. In addition, § 3 is in direct contradiction with §4 below where keeping an electronic version directly available for inspections is contemplated. Please consider removal of paragraph 3.