Update of Implementing Regulation (EU) No 520/2012

Detailed Analysis of Proposed Amendments

21st January 2025

tepsivo

Changed wording in the list of MAH's PV activities

Content of the Pharmacovigilance System Master File (Art. 2, paragraph 2)

"A description of the organisational structure of the marketing authorisation holder, including the list of the site(s) where the following pharmacovigilance activities are undertaken: individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, ***preparation, implementation and maintenance of*** *a risk management plan* ~~*management*~~*, pre- and post-authorisation study management, and management of safety variations* ~~*to*~~ ***of*** *the terms of a marketing authorisation."*

- Text change provides more detailed language regarding the risk management plan, emphasizing its preparation, implementation, and maintenance.
- Additional minor wording adjustment at the bottom of the paragraph *("to" -> "of")*

PSMF to document “significant” deviations only

Maintenance of PV System (Art. 4, paragraph 3)

*“Any **significant** deviations from the pharmacovigilance procedures, their impact and their management shall be documented in the pharmacovigilance system master file until resolved.”*

- Text change from "*Any deviations*" to "*Any significant deviations*".
- **Suggests a shift in focus towards documenting only those deviations that have a notable impact on the pharmacovigilance process.**
- Implies that minor or insignificant deviations may not require documentation in the pharmacovigilance system master file (PSMF). On the other hand, “significant” not defined.

New subcontracting requirements specified

Subcontracting (Art. 6)

- **Completely new paragraph 3** - lists specific elements to be included in subcontracts

" 3. Without prejudice to the second sentence of paragraph 1 and to Article 11(2), the marketing authorisation holder shall include in the subcontracts the following elements:

(a) a clear description of the roles and responsibilities of the third parties to whom pharmacovigilance activities are subcontracted;
(b) obligation of third parties to exchange with the marketing authorisation holder safety data and the method for exchanging safety data, if relevant;

(continues on the next slide)

(continues from the previous slide)

" (c) arrangements for inspection and auditing process of third parties; (d) obligation of the third parties to agree to be audited by or on behalf of marketing authorisation holders and inspected by competent authorities.

This paragraph applies mutatis mutandis to the third parties that subcontract the tasks subcontracted to them by the marketing authorisation holder."

Completely new paragraph 4 - regulates subcontracting of PV activities by 3rd parties

" 4. Third parties shall not subcontract any pharmacovigilance task assigned to them by the marketing authorisation holder without the marketing authorisation holder's written consent."

- **New paragraph 3 regulates what needs to be included in the subcontracts:**

  1) clear description of roles and responsibilities
  2) an obligation to 3rd parties to exchange safety data with the MAH
  3) arrangements for inspections and auditing of 3rd parties
  4) an obligation for 3rd parties to agree to audits by (or on behalf) of MAH and inspections by competent authorities

- **New paragraph 4 defines an obligation for MAH's written consent** in case 3rd parties subcontract pharmacovigilance task(s) assigned to them

Removed mention of signal validation as per Article 21(2)

Compliance management (Art. 11, paragraph 1d)

"...the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions ~~and to validate signals in accordance with Article 21(2);~~"

- Removal of the phrase "*and to validate signals in accordance with Article 21(2)*"
- **The requirement for MAH's to validate signals as per Article 21(2) has been omitted in the new version of the document**

Expanded requirements for MAH / subcontractor audits

Audit (Art. 13, paragraph 1)

~~*"Risk-based audits of the quality system shall be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in Articles 8, 10, 11 and 12 and to determine its effectiveness.*~~

Marketing authorisation holders shall perform regular audits of the quality system at risk-based intervals to ensure that it complies with the requirements set out in Articles 8, 10, 11 and 12 and to determine its effectiveness. The audits shall cover all pharmacovigilance activities for a defined period and verify those activities' conformity with the policies, processes and procedures of the quality system.

Those audits shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited."

- **New, extended wording of requirements for conducting audits of the QMS** relates to:

  1) Audit intervals 2) Scope of audits 3) Compliance with Articles 8, 10, 11 and 12

- **Completely new paragraph 1a** - regulates auditing of subcontractors

> *"1a. Any third party subcontracted to conduct pharmacovigilance tasks in whole or in part on behalf of or in conjunction with marketing authorisation holders shall be audited by or on behalf of marketing authorisation holders and may be inspected by the competent authorities, even if an obligation to agree to an audit and inspection has not been included in the subcontract in accordance with Article 6(3)."*

- Regardless of whether an audit and inspection clause is included in the subcontract, **the subcontractors must be audited and can be inspected**

Expanded requirements for external audits / inspections

Audit (Art. 17, paragraph 1)

"~~Risk-based audits of the quality system shall be performed~~ ***The national competent authorities and the Agency shall perform risk-based audits of the quality system*** *at regular intervals according to a common methodology to ensure that the quality system complies with the requirements set out in Articles 8, 14, 15 and 16 and to* ~~*ensure*~~ ***determine*** *its effectiveness.*

The audits shall cover a defined period and verify the conformity of relevant pharmacovigilance activities concerned by the audit with the policies, processes and procedures of the quality system."

- more specific guidance on **responsible parties** / **purpose and scope** / **audit period**

Responsible parties

New text specifies that the national competent authorities and the Agency are responsible for performing the audits.

Purpose and scope

There is an added emphasis on determining the effectiveness of the quality system.

Additionally, the audits are to verify the conformity of relevant pharmacovigilance activities with the quality system's policies, processes, and procedures.

Audit period

The requirement that audits cover a defined period is introduced, which is not mentioned in the previous version of the document.

Expanded definition of data monitoring obligation

Minimum requirements for the monitoring of data in the Eudravigilance database (Art. 18, paragraphs 2 and 3)

- MAH's responsibility **now to cover data also from other sources than EudraVigilance**

> *"2. Marketing authorisation holders shall monitor the data available in the Eudravigilance database ~~to the extent that they have access to that database.~~* ***together with data from other available sources, as part of their pharmacovigilance responsibilities for data monitoring, signal management and risk assessment.****"*

- **Continuous monitoring requirement is removed from the MAHs**

> *"3. ~~Marketing authorisation holders, the~~ National competent authorities and the Agency shall ensure the continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risks, the potential risks and the need for additional information."*

Broader scope of data monitoring in Eudravigilance

EV Monitoring Identification of changed risks and new risks
(Art. 19(1), third subparagraph)

*"For the purpose of monitoring data in the Eudravigilance database, only signals related to ~~an~~ **a suspected** adverse reaction shall be considered."*

- Term "suspected" is added in relation to adverse reactions
- **The change suggests that a wider range of signals should get attention** - not only confirmed adverse reactions, but also those that are suspected or potential
- Or this could be just administrative change to harmonize the terminology to "suspected adverse event" used in many other documents by the regulators and regulatory authorities

Signal validation requirement paragraph deleted

EV Monitoring Signal Management process (Article 21, paragraph 2)

~~*"Where a marketing authorisation holder detects a new signal when monitoring the Eudravigilance database, it shall validate it and shall forthwith inform the Agency and national competent authorities."*~~

- The clause that required a marketing authorisation holder to validate a new signal and inform the Agency and national competent authorities has been deleted.

Shift in the scope of support related to Eudravigilance

EV Monitoring Signal detection support (Article 23, paragraph 2)

"The Agency shall also ensure appropriate support for ~~the monitoring~~ ***the use*** *of the Eudravigilance database by marketing authorisation holders."*

- Text change from "*the monitoring*" to "*the use*"
- Broadens the scope to possibly encompass all aspects of utilizing the database, which could include accessing, analyzing, and reporting data, in addition to monitoring

Administrative updates in org. names and ISO standards

Use of internationally agreed terminology (Art. 25, paragraphs 1 and 2)

- Update of referenced organizational names

> *"International ~~Conference~~ **Council** on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use"*
> *"European Committee for ~~Standardisation~~ **Standardization**"*

- Update of referenced ISO standards

> *"EN ISO 11615:~~2012~~ **2017**, EN ISO 11616:~~2012~~ **2017**, EN ISO 11238:~~2012~~ **2018**, EN ISO 11239:~~2012~~ **2023**"*

Alternatives to XEVPRM format allowed

Use of internationally agreed formats and standards (Art. 26, paragraph 1)

*"a) the Extended Eudravigilance Medicinal Product Report Message (XEVPRM), ~~which is the format~~ **or another agreed format** for the electronic submission of information on all medicinal products for human use authorised in the Union in accordance with the second subparagraph of Article 57(2) of Regulation (EC) No 726/2004, as published by the Agency"*

- The mention of "another agreed format" in the text **suggests the introduction of flexibility in the submission format**, allowing for alternatives to the XEVPRM as long as they are agreed upon and comply with the specified regulation
- This creates a legislative foundation for the ongoing changes with eAF and upcoming updates with ISO IDMP

ISO standards reference updated

Use of internationally agreed formats and standards (Art. 26, paragraph 2)

- Similarly to the changes in Article 25, the same ISO references in Article 26 are updated

> *"EN ISO 11615:~~2012~~ **2017**, EN ISO 11616:~~2012~~ **2017**, EN ISO 11238:~~2012~~ **2018**, EN ISO 11239:~~2012~~ **2023**"*

Wording changes in the ICSR content requirements

Content of the individual case safety report (Art. 28, paragraph 1)

*"In ~~the case of expedited~~ reporting, the individual case safety report shall include at least ~~an~~ **one** identifiable reporter, ~~an~~ **one** identifiable patient, **at least** one suspected adverse reaction and the medicinal product(s) concerned."*

- The text change generalizes the context to "reporting" without specifying "expedited."
- It also **suggests the possibility of reporting multiple reactions.**
- Highlighting the need to report valid ICSR in all situations.

Literature Reference should be accompanied by DOI

Content of the individual case safety report (Art. 28, paragraph 3)

- **Introduction of DOI requirement** to improve the data quality of the literature ICSRs in EV

> *"...literature reference in accordance with the 'Vancouver style' as developed by the International Committee of Medical Journal Editors (9) for adverse reactions reported in the worldwide literature, including a comprehensive English summary of the article* ***and, if available, the digital object identifier (DOI)***

- Slight change in subparagraph wording

> *(i) concomitant medicinal products, identified in accordance with point (g), which are not suspected to be related to the occurrence of the adverse reaction, and past medical* ~~*drug therapy*~~ ***treatment with medicinal products*** *for the patient (and the parent), where applicable*

RMM implementation updates to be included in PSURs

Content of periodic safety update reports (Art. 34, paragraph 3)

*"The periodic safety update report shall contain **updates on the implementation of the risk minimisation measures and** the results of assessments of the effectiveness of risk minimisation activities relevant to the risk–benefit assessment."*

- While the previous document version only required the results of assessments of the effectiveness of these activities, **the new version emphasizes the need to also report on how these measures are being put into practice**

New definition of study-related obligations for MAH's

PASS (Art. 36, paragraph 5)

- **Completely new paragraph 5 -** regulates submission of study-related documents

> *"The marketing authorisation holder shall enter the study protocol, the abstract of the final study report and the final study report in the electronic post-authorisation study register maintained by the Agency. The marketing authorisation holder shall submit electronically to the register the study protocol before the start of the data collection and the abstract of the final study report within one month after the finalisation of the final study report."*

Change related to description of RMM implementation in PSUR

PSUR - part III of Annex II 'Format of the electronic periodic safety update reports' (point 16.5)

~~*"16.5 Effectiveness of risk minimisation (if applicable)"*~~

"16.5 Implementation of risk minimisation measures and their effectiveness (if applicable)

- With slight text change in the point 16.5, it now mentions not only the effectiveness of risk minimization measures, but emphasizes their implementation

Minor text change related to PASS

PSUR - part III of Annex II 'Format of the electronic periodic safety update reports' (point 16.5)

*"5(f) Any other important milestone applicable to the study, including **the** date of **the** study's registration in the electronic **post-authorisation** study register **maintained by the Agency**.*

- Amended point specifies the type of study and mentions the Agency as the register owner

Unsure about compliance?

Contact us. We will help you establish a truly modern, 100% compliant PV system.

tepsivo

www.tepsivo.com | contact@tepsivo.com