EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

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TARGETED STAKEHOLDER CONSULTATION ON

THE AMENDMENTS TO COMMISSION IMPLEMENTING REGULATION (EU) 520/2012 ON PHARMACOVIGILANCE ACTIVITIES

Period of consultation

31 August to 15 October 2021 (12:00 CET)

Targeted stakeholders

The stakeholders involved in the pharmacovigilance activates.

Objective of the consultation

The Commission Implementing Regulation (IR) on the performance of pharmacovigilance activities[1] was adopted in 2012. It outlines the practical details to be respected by marketing authorisation holders, national competent authorities and the European Medicines Agency (EMA).

As part of the Pharmaceutical Strategy for Europe, the Commission is not only committed to evaluate and review the general pharmaceutical legislation, but also to update and optimise existing implementing measures like the IR. The overall experience with the IR is good. However, following consultation with the EMA and the Pharmacovigilance Risk Assessment Committee, the need for some targeted amendments has been identified to take account of the experience gained and to update certain provisions in view of new technical standards being applied. The aim of this consultation is to inform and consult on those amendments. They focus on the following sections of the IR:

[1] 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 (OJ L 159, 20.6.2012, p. 5) - https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF

- Chapter I - Pharmacovigilance system master file,
- Chapter III - Minimum requirements for the monitoring of data in the Eudravigilance database,
- Chapter IV - Use of terminology, formats and standards,
- Chapter V - Transmission of suspected adverse reactions,
- Chapter VIII - Post-authorisation safety studies.

While this consultation primarily seeks the stakeholders' feedback on those proposed amendments, the Commission welcomes any additional remarks that could improve the application of the IR.

The comments and proposals received will be published and considered in the work leading to the amendments of the IR.

The consultation document

The consultation document includes a detailed outline of the changes that are currently considered.

Protection of personal data

The European institutions are committed to protecting and respecting your privacy. As this service/application collects and further processes personal data, Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, is applicable. More information is available here.

Specific privacy statement

Please consult the Privacy Statement

Additional information

Pharmacovigilance (EC webpage : https://ec.europa.eu/health/human-use/pharmacovigilance_en)

EMA – pilot on monitoring Eudravigilance by marketing authorisation holders

(EMA webpage https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management)

How to submit your contribution

Stakeholders are invited to comment on this consultation by 15 October 2021 at the latest.

Responses should preferably be sent to sante-pharmaceuticals-B5@ec.europa.eu referring in the subject line to "TSC/2021/24 - Targeted stakeholder consultation on the amendments to the Commission Implementing Regulation No (EU) 520/2012".

They can also be sent by post to Directorate-General for Health and Food Safety, Unit B/5, B232 06/085, B-1049 Brussels.

The subject line of the letter or email should contain the reference "TSC/2021/24 - Targeted stakeholder consultation on the amendments to the Commission Implementing Regulation (EU) No 520/2012".

When submitting your response, please include your name and e-mail address and specify if you are responding as an individual or as a representative of an organisation. If you represent an organisation, please indicate its name and category - company/business; public authority (local, regional, national, international); patient organisation; healthcare professional organisation; academic; NGO; other.

Contact details

Any queries about the targeted stakeholder consultation should be sent to: Unit B5 - Medicines: policy, authorisation and monitoring, Directorate-General for Health and Food Safety sante-pharmaceuticals-B5@ec.europa referring to "TSC/2021/24 - Targeted stakeholder consultation on the amendments to the Commission Implementing Regulation No (EU) 520/2012".

Proposed changes to Commission Implementing Regulation (EU) No 520/2012:

Chapter I Pharmacovigilance system master file

The introduction of the pharmacovigilance system master file in 2012 and the related provisions of the Implementing Regulation (EU) No 520/2012 have enhanced efficiency and oversight of pharmacovigilance activities for both the marketing authorisation holders and the regulatory network. However, since EU inspectors have frequently raised findings in the area of contracts / agreements with third parties performing certain pharmacovigilance services for marketing authorisation holders, it is considered that it would be beneficial to strengthen the Implementing Regulation in order to enhance marketing authorisation holders' oversight regarding compliance controls of third parties. This will allow inspectors to check in the contracts between marketing authorisation holders and third parties that risk-based controls are planned for and that they will be actually conducted by the marketing authorisation holder.

Proposed changes

Original text	Proposed changes
CHAPTER I	
Pharmacovigilance system master file	
Article 6	
Subcontracting	
1. The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties. It shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.	1. The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties. It shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.
2. The marketing authorisation holder shall draw up a list of its existing subcontracts between it and the third parties referred to in paragraph 1, specifying the product(s) and territory(ies) concerned.	2. The marketing authorisation holder shall draw up a list of its existing subcontracts between it and the third parties referred to in paragraph 1, specifying the product(s) and territory(ies) concerned.
	3. The marketing authorisation holder shall include in the subcontracts a description of the process in place to ensure third parties are in compliance with the subcontracted pharmacovigilance activities referred to in paragraph 1.

Chapter III Minimum requirements for the monitoring of data in the Eudravigilance database

Chapter III requires marketing authorisation holders, national competent authorities and the Agency to continuously monitor Eudravigilance (EV) data. This should be done in a way that avoids duplicative processes or a proliferation of signals.

It is therefore proposed that the marketing authorisation holders use the Eudravigilance as an additional source of information to support existing pharmacovigilance processes and enhance signals detected through other sources, as well as a resource to evaluate signal detected from other sources. They should not be involved in the validation of signals. This tasks should be left to the regulatory authorities.

Proposed changes

Original text	Proposed changes
CHAPTER III	
Minimum requirements for the monitoring of data in the Eudravigilance database	
Article 18	
General requirements	
2. Marketing authorisation holders shall monitor the data available in the Eudravigilance database to the extent that they have access to that database.	2. Marketing authorisation holders shall monitor the data available in the Eudravigilance database ***in a manner proportionate to the risk, together with other available data sources*** ~~**to the extent that they have access to that database**~~.
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 risk, the potential risks and the need for additional information.	3. ~~**Marketing authorisation holders, t**~~The national competent authorities and the Agency shall ensure the continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information.
Article 21	
Signal management process	
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.	**[deleted]**
Article 23	
Signal detection support	
The Agency shall also ensure appropriate support for the monitoring of the Eudravigilance database by marketing authorisation holders.	The Agency shall also ensure appropriate support for the ~~**monitoring**~~ ***use*** of the Eudravigilance database by marketing authorisation holders.

Chapter IV Use of terminology, formats and standards

In this chapter references to the EN ISO[2] standards will be updated in accordance with the latest applicable version.

In addition, the update will take into account that the use of the ISO ICSR[3] standard based on the ICH E2B(R3)[4] modalities will become mandatory as of 30 June 2022 as per EMA Management Board announcement of December 2019[5]. This includes two of the ISO IDMP[6] standards for routes of administration and pharmaceutical forms for which the terminology is maintained by EDQM[7]. Finally, in Article 26 a reference will be added to HL7 FHIR[8] in

[2] ISO - International Organization for Standardization.
[3] ICSR - individual case safety report.
[4] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs).
[5]https://www.ema.europa.eu/en/documents/other/announcement-ema-management-board-confirmation-mandatory-use-iso-individual-case-report-standard_en.pdf
[6] IDMP – identification of medicinal products.
[7] EDQM - European Directorate for the Quality of Medicines and HealthCare of the Council of Europe.
[8] HL7 FHIR - Health Level Seven Fast Healthcare Interoperability Resources.

support of the electronic submission of medicinal product and substance information based on the ISO IDMP standards.

Chapter V Transmission of suspected adverse reactions

Deletion of the term 'expedited' is proposed to ensure applicability of the minimum reporting requirements to all individual case safety reports (ICSRs). Moreover, the term expedited reporting is no longer regularly used in the EU.

In addition, to improve literature referencing in individual case safety reports, it is proposed that the digital object identifier (DOI) shall also be provided where available by Member States and marketing authorisation holders when reporting suspected adverse reactions.

Proposed changes

Original text	Proposed changes
CHAPTER V	*CHAPTER V*
Transmission of reports of suspected adverse reactions	***Transmission of reports of suspected adverse reactions***
Article 28	*Article 28*
Content of the individual case safety report	**Content of the individual case safety report**
1. Member States and marketing authorisation holders shall ensure that individual case safety reports are as complete as possible and shall communicate the updates of those reports to the Eudravigilance database in an accurate and reliable manner. In the case of expedited reporting, the individual case safety report shall include at least an identifiable reporter, an identifiable patient, one suspected adverse reaction and the medicinal product(s) concerned. […] 3. When reporting suspected adverse reactions, Member States and marketing authorisation holders shall provide all available information on each individual case, including the following: […] (b) literature reference in accordance with the 'Vancouver style' as developed by the International Committee of Medical Journal Editors ([1]) for adverse reactions reported in the worldwide literature, including a comprehensive English summary of the article;	1. Member States and marketing authorisation holders shall ensure that individual case safety reports are as complete as possible and shall communicate the updates of those reports to the Eudravigilance database in an accurate and reliable manner. In the case of ~~**expedited**~~ reporting, the individual case safety report shall include at least an identifiable reporter, an identifiable patient, one suspected adverse reaction and the medicinal **products** concerned. […] 3. When reporting suspected adverse reactions, Member States and marketing authorisation holders shall provide all available information on each individual case, including the following: […] (b) literature reference in accordance with the 'Vancouver style' as developed by the International Committee of Medical Journal Editors (1) for adverse reactions reported in the worldwide literature, including a comprehensive English summary of the article **and where available the Digital Object Identifier (DOI)**;

Chapter VIII Post-authorisation safety studies

The Union electronic register of post-authorisation studies (EU PAS Register) is a public repository of non-interventional post-authorisation studies registered voluntarily by regulatory agencies, marketing authorisation holders, academic institutions and other research organisations. The register is maintained by the EMA. The concept of public registration of post-authorisation studies allows to provide transparency on studies initiated to address questions about the safety of medicinal products and to facilitate peer review of study protocols by third parties.

It is proposed to request that the marketing authorisation holders register and include the study protocol of all imposed non-interventional post-authorisation studies in the EU PAS

Register before the start of the data collection (as defined in Regulation (EU) 520/2012 Article 37(1)).

In case the study protocol contains confidential information, the marketing authorisation holder has two options: 1) to redact the protocol according to the good pharmacovigilance practice (GVP) Module VIII recommendations[9]; or 2) to postpone the public availability of the protocol until the study is finalised (this allows EMA and EU regulators to consult the protocol at an early stage of the study without making it public).

Proposed changes

Original text	Proposed changes
Article 36	*Article 36*
	[…] **[new]** 5. ***The marketing authorisation holder shall register the study 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 results submitted within one month after the finalisation of the final study report.***
Annex III, Format of the final study report, Art 5(f)	*Annex III, Format of the final study report, Art 5(f)*
[…] any other important milestone applicable to the study, including date of study registration in the electronic study register.	[…] any other important milestone applicable to the study, including date of study registration in the electronic ***post-authorisation*** study register ***maintained by the Agency***.

[9] Heads of Medicines Agency; European Medicines Agency, *Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies*, EMA/813938/2011 Rev 3, 9 October 2017 - https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf