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Recording by marketing authorisation holders of information on suspected adverse reactions held in EudraVigilance

Note for clarification

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1. Introduction

The 2010 pharmacovigilance legislation has certain high level objectives, which included the reduction of the burden of adverse drug reactions (ADRs) while reducing any unnecessary administrative burden resulting from pharmacovigilance activities. The new provisions relating to EudraVigilance and simplified ADR reporting were central measures in terms of reducing administrative burden.

With the launch of the new EudraVigilance system on 22 November 2017[1], the simplified (electronic) reporting of suspected adverse reactions related to medicines in the format of Individual Case Safety Reports (ICSRs) by national Competent Authorities (NCAs) and marketing authorisation holders (MAHs) to the EudraVigilance database became mandatory[2]. Based on this simplification, NCAs and MAHs no longer have to report to each other directly, thus reducing duplicative reporting.

Furthermore, in line with the provisions of Article 24(2), 5th subparagraph of Regulation EC (No) 726/2004, EudraVigilance was made accessible to MAHs to "*the extent necessary for them to comply with their pharmacovigilance obligations*". The levels of access are set out in the EudraVigilance Access Policy[3].

2. Purpose of this document

Taking into account initial experience in operating the simplified reporting rules and MAHs' access to EudraVigilance, the pharmaceutical industry asked for clarification of the obligations of MAHs to record information on suspected adverse reactions they access in EudraVigilance.

The purpose of this note for clarification is to address this aspect with the aim to provide MAHs clear guidance and legal certainty about their pharmacovigilance obligations in the EEA in the context of the pharmaceutical legislation for medicinal products for human use so they can adapt their processes and procedures as necessary and inspections can be conducted in a consistent manner.
Where applicable, a clarification of the obligations will also allow MAHs to adapt their processes as regards their reporting obligations of suspected adverse reactions in third countries.

3. Recording and reporting principles

This section summarises key principles of the recording and reporting of information on suspected adverse reactions related to medicines by MAHs:

- Article 12(1) of the Commission Implementing Regulation (EU) No 520/2012 provides that "*Marketing authorisation holders shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow for accurate reporting, interpretation and verification of that information. (…)*"

[1] Following the successful audit of the new EudraVigilance system in accordance with Article 24 of Regulation (EC) 726/2004, the EMA Management Board confirmed on 22 May 2017 that the full functionality of the EudraVigilance database had been achieved and the system met the defined functional specifications. The simplified electronic reporting of suspected adverse reactions related to medicines by NCAs and MAHs to EudraVigilance became mandatory six months after the functionalities of the EudraVigilance database had been established and announced by the Agency i.e. 22 November 2017.

[2] On 22 November 2017, the obligations set forth in the following legal provisions:

- Section 1 "Recording and reporting of suspected adverse reactions" of Chapter 3 "Recording, reporting and assessment of pharmacovigilance data" under Title IX "Pharmacovigilance" of Directive 2001/83/EC3, and
- Articles 24(4), 28(1), 28a(1)(c) and 28c(1) of Chapter 3 "Pharmacovigilance" under Title II "Authorisation and supervision of medicinal products for human use" of Regulation (EC) No 726/2004

became applicable to the mandatory electronic reporting through EudraVigilance.

[3] European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use (EudraVigilance Access Policy) (EMA/759287/2009 Revision 3*).

- Article 107(1) of Directive 2001/83/EC provides that "*Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study.*" As regards EudraVigilance, the database is to be considered as the 'target' for such reporting, where ICSRs should be stored, and not as the source of new case reports to be (again) recorded and reported.
- Article 107a of Directive 2001/83/EC sets out the reporting requirements of suspected adverse reactions by Member States. Article 107a(4), 3rd subparagraph, provides that "*Marketing authorisation holders shall access those reports through the Eudravigilance database*". This underlines that MAHs should use these newly recorded case reports in EudraVigilance to enrich and supplement their own databases and to fulfil their obligations with regard to the monitoring of the safety of medicines and the detection of any changes to their benefit-risk balance.
- Article 18(2) of the Commission Implementing Regulation (EU) No 520/2012 sets out that "*Marketing authorisation holders shall monitor the data available in the Eudravigilance database to the extent that they have access to that database*". The monitoring of the safety of medicines and the detection of any changes to their risk-benefit balance in the context of data held in EudraVigilance is therefore provided for.
- A key objective of the 2010 pharmacovigilance legislation was the simplification of adverse reaction reporting. As stated in preamble 9 of the Commission Implementing Regulation (EC) No 520/2012, "*pharmacovigilance activities rely increasingly on the periodic monitoring of large databases, such as the EudraVigilance database. Whereas the EudraVigilance database is expected to be a major source of pharmacovigilance information, account should also be taken of pharmacovigilance information coming from other sources*". Duplication of efforts in recording adverse reactions reports already recorded in EudraVigilance should therefore be limited thus freeing resources to focus on the monitoring of information coming from other sources relevant to the safety of medicines.

3.1. Recording of suspected adverse reactions related to medicines accessed "prospectively" by MAHs as of 22 November 2017

As regards the recording of suspected adverse reactions related to medicines accessed "prospectively" by MAHs as of 22 November 2017:

a. MAHs should record all individual cases of suspected adverse reactions for substances of medicinal products, for which they hold a marketing authorisation in the European Economic Area (EEA) and that are submitted by NCAs in EEA Member States to EudraVigilance. This applies to all individual cases originating within the EEA and where the MAH cannot exclude ownership of the medicinal product reported (suspect or interacting) as outlined under point c.

b. MAHs should decide whether they record individual cases of suspected adverse reactions for substances of medicinal products for which they hold a marketing authorisation in the EEA and which were submitted by other MAHs to EudraVigilance. The decision should be based on the processes necessary for the MAHs to comply with their pharmacovigilance obligations based on the criteria set out in Annex A. The recording or not of these ICSRs should be documented as part of the pharmacovigilance system used by the MAH to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC and designed to monitor the safety of authorised medicinal products and to detect any change to their risk-benefit balance. This applies to all individual cases where the

MAH cannot exclude ownership of the medicinal product reported (suspect or interacting) as outlined under point c.

c. The exclusion of ownership criteria are based on the principles detailed in Chapter VI.C.2.2 of GVP Module VI.

3.2. Recording of suspected adverse reactions related to medicines accessed "retrospectively" by MAHs as of 22 November 2017

As regards the obligations of MAHs to screen and record individual cases of suspected adverse reactions related to medicines, which were reported to EudraVigilance prior to 22 November 2017:

a. MAHs are not obliged to retrospectively screen EudraVigilance for individual cases that are not yet recorded in their databases to complement or reconcile the respective internal information.

b. MAHs are not obliged to record in their databases individual cases submitted to EudraVigilance prior to 22 November 2017 of which they gained knowledge retrospectively as part of their signal management or other pharmacovigilance obligations.

c. This does not preclude a MAH choosing to reconcile and record individual cases identified in EudraVigilance in the context of the assessment of a safety issue, e.g. for the end-point of the signal management or safety monitoring activities such as the identification of a new risk or adverse drug reaction, or change in the status of a known risk or adverse drug reaction as part of a validated signal.

4. Conclusion

The 2010 pharmacovigilance legislation and the changes it introduced for MAHs with regard to processes and obligations to be fulfilled applied prospectively and not retrospectively. Hence, it does not require MAHs to revisit or supplement recordings that predate its entering into application i.e. 22 November 2017 in relation to EudraVigilance.

Article 107 of Directive 2001/83/EC sets out the process of how companies should record and report suspected adverse reactions. In this context EudraVigilance is presented as the 'target' for such reporting, where ICSRs should be stored, and not as the source of new case reports to be (again) reported and recorded.

This does not exclude that MAHs may use newly recorded case reports in EudraVigilance to enrich and supplement their own databases and to fulfil their obligations with regard to the monitoring of the safety of medicines and the detection of any changes to their benefit-risk balance. This is underlined by the fact that MAHs shall access reports submitted by NCAs directly through the EudraVigilance database (Article 107a(4) of Directive 2001/83/EC). With regards to the recording of reports submitted by other MAHs directly through EudraVigilance, the criteria set out in Annex A provide further clarification.

Annex A

Pharmacovigilance obligations based on Title IX of Directive 2001/83/EC with focus on the safety monitoring and benefit-risk assessment of medicinal products

In accordance with Article 104(1) of Directive 2001/83/EC, the MAH shall operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks. Furthermore, the MAH shall by means of the pharmacovigilance system evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary (Article 104(2) of Directive 2001/83/EC).

As part of the pharmacovigilance system operated by the MAH in accordance with Article 104(3) of the Directive, MAHs should:

- operate a risk management system for each medicinal product[4];
- monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a of the Directive;
- update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

In support of the pharmacovigilance system operated by MAHs, this annex sets out the criteria as to when MAHs should record individual cases of suspected adverse reactions they access in EudraVigilance, which were submitted by other MAHs directly to EudraVigilance.

The criteria are based on the processes necessary for MAHs to comply with their pharmacovigilance obligations listed in Title IX of Directive 2001/83/EC with focus on the safety monitoring and benefit-risk assessment of medicinal products and take into account that, in line with Article 24 of Regulation EC (No) 726/2004, EudraVigilance is accessible to MAHs to "the extent necessary for them to comply with their pharmacovigilance obligations".

Recording and reporting of suspected adverse reactions

Article 107 of Directive 2001/83/EC sets out the obligations of MAHs as regards the recording and reporting of suspected adverse reactions as well as the procedures to be operated by the MAH to:

- obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;
- collect follow-up information on these reports and submit the updates to the EudraVigilance;
- collaborate with the Agency and the Member States in the detection of duplicates of suspected adverse reaction reports.

Article 107(3) of the Directive provides that "*for medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, MAHs shall not be required to report to EudraVigilance the suspected adverse reactions*

[4] Article 104a 1 of Directive 2001/83/EC: Without prejudice to paragraphs 2, 3 and 4 of this Article, holders of marketing authorisations granted before 21 July 2012 shall, by way of derogation from Article 104(3)(c), not be required to operate a risk management system for each medicinal product.

recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions".

Details of these procedures are further described in the Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products.

The Commission Implementing Regulation (EC) No 520/2012, chapter V, sets out the format and content of Individual Case Safety Reports for reporting of suspected adverse reactions to EudraVigilance.

Criterion for recording and reporting of suspected adverse reactions to EudraVigilance

- As part of the pharmacovigilance systems that MAHs operate and for the purpose of reporting of suspected adverse reactions to EudraVigilance, MAHs are not obliged to record individual cases of suspected adverse reactions, which are submitted by other MAHs directly to EudraVigilance.
- Article 107 of Directive 2001/83/EC sets out the process of how MAHs should record and report suspected adverse reactions. In this context EudraVigilance is presented as the 'target' for such reporting, where information on ICSRs should be stored, and not as the source of new case reports to be (again) reported and recorded.

Periodic Safety Update Reports (PSURs)

The requirements for preparing and submitting PSURs by MAHs are provided for in Article 107b of Directive 2001/83/EC. The Commission Implementing Regulation (EC) No 520/2012, chapter VII, sets out the content and format of PSURs.
Details on the preparation of PSURs are further outlined in Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report with further clarification provided in the Explanatory Note to GVP VII.

Criterion for preparation of PSURs

- As part of the pharmacovigilance systems that MAHs operate and for the purpose of the preparation of PSURs, MAHs are not obliged to record individual cases of suspected adverse reactions, which are submitted by other MAHs directly to EudraVigilance.
- MAHs should follow the guidance set out in the Explanatory Note to GVP VII, chapter 9.5 "Use of EudraVigilance data by MAHs during the preparation of PSURs".

Signal Detection

The principles of signal detection are set out in Article 107h of Directive 2001/83/EC with the obligations of MAHs further defined in the Commission Implementing Regulation (EU) No 520/2012, chapter III, "Minimum requirements for the monitoring of data in the Eudravigilance database". Article 18(2) of the Implementing Regulation (EC) 520/2012 requires MAHs to "monitor the data available in EudraVigilance to the extent that they have access to that database".

The signal management process and the communication of validated signals are further outlined in the Guideline on good pharmacovigilance practices (GVP): Module IX – Signal management.

Criterion for signal detection and management

- As part of the pharmacovigilance system that MAHs operate and for the purpose of signal detection, MAHs are not obliged to record individual cases of suspected adverse reactions, which are submitted by other MAHs directly to EudraVigilance.
- The Commission Implementing Regulation (EU) No 520/2012 requires MAHs to monitor the data available in EudraVigilance to the extent that they have access to that database. The monitoring of the safety of medicines and the detection of any changes to their risk-benefit balance is therefore provided for.