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DRAFT detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency

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Table of contents

Introduction

1.1. Scope

Scientific and medical literature is an important source of information on suspected adverse reaction case reports (also referred to as individual case safety reports). Currently, for active substances included in more than one medicinal product for human use, literature cases are reported in adverse reaction case reports in a duplicative way by marketing-authorisation holders (MAHs) in the European Economic Area (EEA), which is based on their obligation to monitor scientific and medical literature as outlined in the Good Pharmacovigilance Practices (GVP) guideline, Module VI 'Management and reporting of adverse reactions to medicinal products'.

To enhance the efficiency of reporting and to provide a simplification for pharmaceutical industry, Article 27 of Regulation (EC) 726/2004[1] sets out the following:

1. The Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It shall publish a list of active substances being monitored and the medical literature subject to this monitoring.
2. The Agency shall enter into the EudraVigilance database relevant information from the selected medical literature.
3. The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database.

In accordance with Article 107, paragraph 3 of Directive 2001/83/EC, for medicinal products containing the active substances referred to in the list of publications monitored by the European Medicines Agency (EMA) pursuant to Article 27 of Regulation (EC) No 726/2004, MAHs shall not be required to report to the EudraVigilance database the suspected adverse reactions recorded in the listed medical literature. *However, MAHs shall monitor all other medical literature and report any suspected adverse reactions.*

Furthermore, Article 28 of Regulation 726/2004 states that the obligations of MAHs and of Member States laid down in Articles 107 and 107a of Directive 2001/83/EC shall apply to the recording and reporting of suspected adverse reactions for medicinal products for human use authorised in accordance with this Regulation.

For the purpose of the literature-monitoring services to be provided by the Agency in line with Article 27 of Regulation (EC) 726/2004, the structures and processes as outlined in GVP module VI apply accordingly, in particular the provisions set out in chapter *VI.C.2.2.3. 'Case reports published in the scientific and medical literature'* and in chapter VI. Appendix 2 *'Detailed guidance on the monitoring of scientific and medical literature'*.

Key principles for the literature-monitoring services that were raised by pharmaceutical industry and that have been reflected in this detailed guide are summarised as follows:

- Alleviate the burden on maximum number of MAHs.
- Innovative medicinal products should not be covered.

[1] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Consolidated version: 05/06/2013).

- Avoid partial service that would necessitate duplicative efforts by MAHs.
- Provide quality controlled literature-monitoring services.
- Establish a process so that MAHs can comply with the worldwide regulatory requirements.

In summary, this detailed guide describes the technical aspects of the literature-monitoring services to be provided by the Agency in line with the requirements set out in Article 27 of Regulation (EC) 726/2004 and GVP module VI.

1.2. Literature-monitoring services

The Agency has decided to outsource the monitoring of scientific and medical literature and the entry of relevant information into EudraVigilance to a service provider.

2. Monitoring of selected medical literature for reports of suspected adverse reactions

2.1. Active substances that the Agency is monitoring

The Agency has defined a range of substances including herbal substances for the purpose of the literature-monitoring services. These substances have been selected on the basis of being active ingredients for medicinal products with high numbers of MAHs in the EU and are grouped as follows:

i. Substances by active moiety including e.g. salts, esters as well as combinations (hereafter referred to as substance groups)[2].

ii. Herbal substances by genus[3].

The total number of substance groups to be included in the literature-monitoring services is depending on the allocated budget[4] and may be subject to annual updates and changes by the Agency. Updates to the list of substances are being published in October each year becoming effective in January thereafter to allow MAHs a timely adjustment of their business processes in line with the substances being monitored by the Agency.

2.2. Scientific and medical literature that the Agency is monitoring

The Agency's monitoring services focus on scientific and medical literature as referred to in GVP module VI (such as articles from periodicals, journals, case studies, reports, conference proceedings, media releases or similar products):

i. For the purpose of the identification and retrieval of any new information on:

- suspected adverse reactions in humans in relation to spontaneous reports;
- reports of single or multiple cases of suspected adverse reactions from studies including post-authorisation study results (with the exclusion of suspected adverse reactions from interventional clinical trials);
- reports of single or multiple cases of suspected adverse reactions from organised data collection systems referring to registries, post-approval named patient or compassionate use

[2] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500163678.pdf
[3] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500163679.pdf
[4] The first list of substance/herbal substance groups subject to the Agency's literature-monitoring services will be published in October 2014.

programmes, other patient support and disease management programmes, surveys of patients or healthcare providers and information gathering on efficacy or patients' compliance;

- situations of lack of therapeutic efficacy, use of a medicinal product during pregnancy or breastfeeding as well as off-label use, misuse, abuse, overdose, medication errors and occupational exposure with and without association of a suspected adverse reaction.

i. The scope refers to widely used and daily updated scientific and medical literature reference databases in line with those referred to in GVP module VI as well as specialised databases, where deemed necessary (e.g. for herbal substances).

ii. The supplied literature needs to be accurate and exhaustive thereby avoiding the necessity for duplicate screening efforts by MAHs.

Non-indexed local journals are excluded from the Agency's monitoring activities and remain under the responsibility of the MAHs.

The Agency publishes the list of the medical literature with the name, type and short description of the journal/reference database(s) as well as the number and the names of the journals covered by the Agency's services. Potential updates are announced in October of each year, which are becoming effective in January thereafter to allow MAHs a timely adjustment of their business processes.

3. Screening of selected scientific and medical literature and recording of all screening activities

3.1. Screening of selected scientific and medical literature

In accordance with GVP module VI, the literature-monitoring services provide for a daily review and assessment of the screened scientific and medical literature to identify:

- suspected adverse reactions in humans in relation to spontaneous reports;
- reports of single or multiple cases of suspected adverse reactions from studies including study results (with the exclusion of suspected adverse reactions from interventional clinical trials);
- situations of lack of therapeutic efficacy, use of a medicinal product during pregnancy or breastfeeding as well as off-label use, misuse, abuse, overdose, medication errors and occupational exposure with and without association of a suspected adverse reaction.

The screening includes all suspected serious and non-serious adverse reactions.

Daily refers to calendar days with the exception of weekends.

Search constructions for the screening of the literature follow the principles outlined in GVP module VI. App2.3 'Database Searches' and are being customised by substance groups taking into account the following:

i. The substance groups search has to be exhaustive, where necessary additional search by trade name (in all their variants) is also to be taken into account. The most comprehensive search strategy is applied by substance covering all substance variations as defined by each substance group.

ii. The search is performed at full text level taking into account that it may be appropriate to limit the search to a major mention (substance or medicinal product indexed to title, abstractor main topic of article) to increase search precision.

iii. Results are to be reproducible and tracked.

Search constructions for each substance group are listed and made available at the EudraVigilance restricted website accessible to the Agency, the European Commission, national competent authorities in EEA Member States and MAHs in the EEA. Search constructions are routinely updated and maintained where necessary to improve search precision and to align with any updates to the substance groups as referred to in chapter 2.1.

3.2. Recording of all screening activities

The screening of the medical and scientific literature is recorded in full based on the following:

- The name of the reference database(s).
- The date and time when searches where performed.
- The exact search string for each substance and related substance group.
- The literature that was retrieved and reviewed with clear and identifiable literature references incl. a Document Object Identifier (DOI) or where not available a uniform resource locator (URL) or alternative identifier5.
- The criteria upon which literature reports were excluded or included for further case processing and creation of Individual Case Safety Reports (ICSRs) in EudraVigilance including a classification if the literature refers to serious and/or non-serious adverse reactions and the specification of the primary source country.
- A flag to highlight literature that refers to situations of lack of therapeutic efficacy, use of a medicinal product during pregnancy or breastfeeding as well as off-label use, misuse, abuse, overdose, medication errors and occupational exposure with and without association of a suspected adverse reaction.

Search results based on the execution of scripts are made publicly accessible on a daily basis. The outputs are provided in a tabular, user-friendly format on the EudraVgilance restricted website.

Records of literature searches including the results of the review of the articles returned from searches are maintained until 10 years in accordance with the requirements described in Article 16 of the Commission Implementing Regulation (EU) No 520/2012[6]. A record of the search construction, the database used and the date the search was run is retained. In addition, the results of the search are retained for same period of time as described in Article 16, particularly in the event of zero results. The decisions made on the results, are also retained.

[5] Note: The Document Object Identifier (DOI) is not unique to an individual case safety report, which is characterised by the world-wide unique case identifier. Where a literature article refers to several individual cases, the same DOI is referenced in these cases.

[6] 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.

4. Processing of individual cases related to suspected adverse reactions identified as a result of the scientific and medical literature-screening activities

4.1.1. Processing of individual cases related to suspected adverse reactions

All valid individual cases for the substance groups as described in chapter 2.1. , which are identified as a result of the screening of the scientific and medical literature, are processed within the following timelines:

- Suspected serious adverse reactions are entered in EudraVigilance immediately and no later than seven calendar days from day zero.
- Non-serious adverse reactions are entered in EudraVigilance within three calendar weeks from day zero.

Day zero for the timelines related to the entry of individual cases in EudraVigilance refers to the date on which the Agency's service provider becomes aware of a publication containing the minimum information for an ICSR to be reportable in line with the principles set out in GVP module VI, chapter VI. App2.7 'Day zero'.

The Agency will announce when the entry of individual cases related to non-serious adverse reactions will be initiated. This refers to the reporting arrangements as set out in GVP module, VI chapter VI.C.4.2. 'Final arrangements'[7]. Individual cases related to purely non-serious adverse reactions, with a primary-source country outside the EEA are excluded from EudraVigilance.

Valid ICSRs are created in accordance with the modalities detailed in GVP module VI (chapters VI.B.2. 'Validation of reports', VI.B.7 'Reporting of ICSRs', VI.B.8 'Reporting modalities', VI.C 'Operation of the EU Network', VI, Appendix 3 'Modalities for reporting') and in line with Articles 27, 28 and 29 of the Commission Implementing Regulation (EU) 520/2012 including a reference to the DOI or if not available, the URL or other unique identifier for the literature article.

ICSRs are generated in English and in compliance with EU personal data protection legislation[8].

4.1.2. Follow-up of individual cases related to suspected adverse reactions identified as a result of the scientific and medical literature screening activities

A process is put in place by the Agency that ensures that individual cases are followed-up with the publication author(s) as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases in line with the GVP module VI.

One attempt to follow-up with the primary author(s) is made for serious adverse reactions based on a risk-based approach. This refers to individual cases, where the outcome is not known, where pre-defined clinical information is missing as regards important medical events or for both and for serious cases where not all of the minimum reporting criteria are available.

[7] This relates to the announcement that the EudraVigilance functionalities have been achieved following the successful outcome of the independent audit as referred to in Article 24 of Regulation (EC) 726/2004.
[8] Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data.

Important medical events refer to the Important Medical Events (IMEs) list maintained by the EMA referenced on the EudraVigilance website.

Any attempts to obtain follow-up information are documented in a tracking table for tracking purposes.

New information related to ICSRs is processed in line with GVP module VI, chapter VI.B.3. 'Follow-up of reports' within seven calendar days following receipt of new information related to suspected serious adverse reactions. Day zero refers to the date of receipt of any new follow-up information.

Where a MAH obtains additional new information outside the follow-up process operated by the Agency, the MAH should send a follow-up case with the new information to EudraVigilance.

4.1.3. Provision of individual cases related to suspected adverse reactions identified as a result of the scientific and medical literature-screening activities to EEA Member States

The ICSRs, once entered in EudraVigilance, are transmitted electronically within one calendar day to the national Competent Authority in EEA Member States based on the primary source country or where not available to the country of the primary author of the article.

The reports of suspected adverse reactions originating from within the EEA are transmitted to Member States in line with the 'Reporting requirements of ICSRs applicable to marketing authorisation holders during the interim period' (Doc. Ref. EMA/321386/2012, in the latest version) until the provisions set out in GVP module, VI chapter VI.C.4.2. 'Final arrangements' come into force.

Related copies of literature article(s) and where applicable, translations thereof, are entered into the EudraVigilance related literature repository (with the file name of the literature matching the world-wide unique case identifier assigned to the created individual case as outlined in GVP Module VI chapter VI. App2.10 'Electronic submission of copies of articles published in the scientific and medical literature'). The copies of the articles are accessible in the literature repository to the national competent authorities in EEA Member States. The literature repository allows access to copies of articles by means of the worldwide unique case identifier of the corresponding ICSR.

4.1.4. Provision of individual cases related to suspected adverse reactions identified as a result of the scientific and medical literature-screening activities to MAHs

The ICSRs entered in EudraVigilance as a result of the scientific and medical literature screening activities are published daily in electronic format for download by MAHs. Daily refers to calendar days with the exception of weekends.

A listing is provided to MAHs for ease of identification of applicable ICSRs at the EudraVigilance restricted website. The list contains the related substance(s) and substance group, the world-wide unique case identification number, the reference to the relevant literature reference including the DOI or URL or an alternative unique reference (if the DOI is not available), the primary source country, a seriousness flag as well as the receive date and receipt date to allow the determination the initial or follow-up status of the ICSR.

5. Quality management

Well-defined and regularly audited quality management practices are put in place to ensure that the service provider operates to consistently high levels of quality, efficiency and cost-effectiveness. Records are maintained in accordance with the provisions of ISO 15489.

Measures are put in place to facilitate performance monitoring, the assessment whether performance meets the Agency's stakeholders' needs and that allow taking appropriate action such as understanding and extending features of good performance and correcting areas of underperformance. Those measures are further defined as part of a Service Level Agreement between the Agency and the service provider.

A survey to be conducted at six monthly intervals of a sample of MAHs and national competent authorities in EEA Member States is to aid the identification of potential areas of improvement and to improve performance if required.

In addition, a service desk is provided to assist in dealing with enquiries from MAHs and national competent authorities in EEA Member States.

The Agency will initiate a two yearly, independent audit of the service provider's internal quality management and control systems and of the services provided to assess their effectiveness with a view to bringing about continuous improvement. The audit is to be performed by an independent auditor appointed by the Agency. The first audit of the literature screening process will be conducted within six months following the successful completion of a literature monitoring pilot with MAHs and national competent authorities in EEA Member States.

6. Use of formats, standards and terminology

The entry of identified ICSRs in EudraVigilance and the handling of related copies of literature article(s) is based on a phased implementation approach, as follows.

In a first phase:

i. use of the current ICH E2B(R2) format and related terminologies (as referred to in Article 25, paragraph 1a) and 1b) as well as Article 26, paragraphs 1a), 1b) and 1c) of the Commission Implementing Regulation (EU) 520/2012, and;

ii. submission and loading of electronic copies of literature articles into the EudraVigilance literature repository so that the articles are accessible to the EMA and all national competent authorities in EEA Member States responsible for medicines for human use. Supported file formats are: doc; htm; pdf; docx; html.

In a second phase:

i. use of the ISO 27953-2:2011 standard 'Health Informatics, Individual case safety reports (ICSRs) in pharmacovigilance — Part 2: Human pharmaceutical reporting requirements for ICSR' as referred to in Article 26, paragraph 2.a) and related terminology as outlined in Article 25, paragraph 1.a) to 1.g) of the Commission Implementing Regulation (EU) 520/2012. The ISO ICSR standard will allow attaching copies of literature articles directly to the applicable ICSRs.