PHV-4 Version 8 ELECTRONIC REPORTING OF ADVERSE DRUG REACTIONS

As of 8th April 2022, this Guideline shall supersede PHV-4 version 7.

The Guideline is issued on the basis and in accordance with the provision of Section 91 paragraph 4 and Section 93a of Act no. 378/2007 Coll., on Pharmaceuticals. **The Guideline is legally binding.**

Amendments in this Guideline:

- Repeal the obligation to submit to SÚKL the contact details of the person responsible for ICSR reporting
- Modification of information on local requirements for literature reports

1. Introduction and general provisions

1.1 Purpose of the Guideline specification

The Guideline specifies the rules of electronic exchange of adverse reaction reports concerning medicines for human use via the EudraVigilance (EV) system. The Guideline is intended for marketing authorization holders and organizations that perform electronic reporting of adverse reaction reports (in format E2B (R2) or E2B (R3)) on behalf of marketing authorization holders. The content and general rules of reporting are governed by the applicable legal regulations and guidance of SÚKL and of the Agency.

1.2 List of abbreviations

ACK acknowledgement message sent by a report receiver to a report sender
ADR adverse drug reaction
CDNÚ SÚKL ADR database
EEA European Economic Area
EMA European Medicines Agency, hereinafter also the "Agency"
EV EudraVigilance
EVCTM EudraVigilance Clinical Trial Module
EVPM EudraVigilance Post-Authorisation Module
FU follow up report
GVP Guideline on good pharmacovigilance practices
ICH International Conference on Harmonization
ICSRs Individual Case Safety Reports
ID Identifier in the EudraVigilance system
ISO International Organization for Standardization
MAH Marketing Authorisation Holder
QPPV Qualified Person for Pharmacovigilance
SÚKL – State Institute for Drug Control
XEVMPD – Extended EudraVigilance Medicinal Product Dictionary

1.3 Legislative and standardisation base of the guideline

Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts, as amended (hereinafter the "Pharmaceuticals Act" or the "Act")
Decree No. 226/2008 Coll., on good clinical practice and detailed conditions of clinical trials on medicinal products
Decree No. 228/2008 Coll., on the marketing authorisation of medicinal products, as amended
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

Guideline on good pharmacovigilance practices: Annex 1 - Definitions
Guideline on Good Pharmacovigilance Practices Module VI: Management and reporting of adverse reactions to medicinal products
Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs) including other EU guidelines and ICH standards (in particular E2B, M1 and M2).
ICH Harmonised Tripartite Guideline Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports E2B(R2)
Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs): E2B(R3) Data Elements and Message Specification
EU Individual Case Safety Report (ICSR) Implementation Guide
SÚKL guideline KLH-21– Reporting adverse reactions to human medicinal products arising from clinical trials
SÚKL Guideline PHV-6 - SÚKL requirements for reporting changes in the PSMF, for appointing the qualified person for pharmacovigilance and for appointing the contact person for pharmacovigilance issues in the Czech Republic
Further details can be found in the relevant ongoing Q&A documents published on the EMA website.

2. Clarification of definitions in the area of the electronic interchange of reports

EudraVigilance – a database and a system for electronic interchange of reports within the EEA, established and managed by EMA
Individual Case Safety Report (ICSR) – a report of suspected adverse drug reaction
Acknowledgement (ACK) – an ichicsrack report in the xml format – a report sent by the recipient of ICSR to the sender, confirming successful processing of the sent report (code 01 for R2 format, AA - CA for R3 format) or informing about errors preventing the processing of this report (code 02 or 03 respectively for R2 format and AE – CR or AR for R3 format)
Follow-up of the report – a complement of the new important additional information to the initially reported ADR report
Art. 57 Database (part of XEVMPD) – EMA database in which structured and quality assured information on medicinal products authorised in the EU is collected, the information is reported by the MAHs to the database, it contains also data which are required in accordance with the Article 57(2) of the Regulation (EC) No. 726/2004
CDNÚ - Central ADR database – a SÚKL database integrated with a gateway, capable of a fully automated electronic interchange of reports with EMA.
MAH – a marketing authorisation holder of a medicinal product
Re-routing of ICSRs – an automatic process done by EMA during which ICSRs sent to EV database by MAHs are re-routed (re-sent) to particular NCAs in the EEA down by the country of a (main) reporter.

3. Method and particulars of reporting

An electronic report shall mean an individual case safety report in the format defined by the ICH E2B(R2) guideline, the individual items of which are described by the ICH M2 guideline and specified by EMA guidance. Reports which do not comply with this definition shall be, for the purposes of this guideline, referred to as **non-electronic reports,** even if they are sent electronically (e.g. by e-mail).

Electronic reporting is defined as the transfer of the ichicsr message in the xml format between the sender and recipient using the EudraVigilance system, and subsequent transfer of the Acknowledgement (ACK) from the recipient to the sender. The ACK format is also defined by the ICH M2 guideline and E2B(R3) IG.
Electronic report submission is considered successful and completed only if the sender of the message or report receives an ACK in the correct format showing the value of 01 for message sent in E2B(R2) format and AA – CA for message sent E2B(R3) in the relevant items of the ACK message.

Since 22 November 2017 (the date of the new EudraVigilance system go-live) all ADR reports received from HCPs or consumers by SÚKL **are sent to EudraVigilance database** from the production ID CZSUKL in accordance with the rules given by the Pharmaceuticals Act § 93c (3) as follows:

All CZ serious reports	**Within 15 days after report receipt**
All CZ non-serious reports	**Within 90 days after report receipt**

Since 22 November 2017 SÚKL **has not resent any ADR reports** received by SÚKL from HCPs or consumers to MAHs. These reports are available for MAHs in EudraVigilance database in the extent given by EV Access Policy.

At the same time since 22 November 2017 SÚKL has not accepted any ICSRs sent by MAHs, MAHs submit their ICSRs directly to the EV database (to ID EVHUMAN for reports to EVPM module and to ID EVCTMPROD for reports to EVCTM module) within the scope of the centralised reporting. These reports are obtained by SÚKL using the EMA re-routing function.

When processing reports which are originated in CZ and are submitted to the European database in accordance with §93a (2) of the Pharmaceuticals Act, SÚKL shall apply all the rules for their processing and quality assessment as specified in GVP Module VI (the version in force).
All SUSARs originated from CTs are to be submitted to EudraVigilance database directly (to EVCTM). Rules for reporting from CT follow the Guideline KLH-21 and the Clinical Trial Directive 2001/20/EC transposed to the legislation. Rules applicable to reports arising from clinical trials shall be governed by guideline KLH-21 and by Directive 2001/20/EC (Clinical Trial Directive) as transposed in the national legislation.

According to guideline PHV-6 MAH is newly obliged to appoint a contact person for pharmacovigilance issues in the Czech Republic. Their basic responsibility is to ensure communication with SÚKL, even in the area concerning the ICSR reporting, therefore the obligation to provide to SÚKL information on the person responsible for ICSRs submission is cancelled. Primary contact for issues regarding ICSR reporting from the Czech Republic (ICSR data quality issues, technical problems, Follow-up requests from SÚKL) will hence be the contact person for pharmacovigilance issues.

4. Specific requirements for the reports originated in CZ:

4.1 Case narrative in reporter's native language

For ICSRs sent in new ISO format E2B (R3) it is required by SÚKL to provide information on Case narrative and Reaction/Event as reported in native reporter's language in case they are available to MAH. Such information should be given in the form of verbatim text according to the report source documents in appropriate E2B (R3) fields (Case Summary and Reporter's comments Text (H.5.r.1a) and Reaction/Event as reported by the Primary Source in Native Language (E.i.1.1a). It is also important to add the language codes to both fields. – in H.5.r.1b and E.i.1.1b fields.
The obligation to fill in case narrative in the native language of the reporter (field H.5.r.1a Case Summary and Reporter's Comments) does not apply to reports from the literature. In this case, a literary article is considered as a sufficient description of the case in the native language; it is not necessary to include it or its summary in the report.
The obligation to fill in the reactions as reported by the reporter (field E.i.1.1a Reaction / Event) in the native language of the reporter, however, still applies to reports from the literature.

The requirement is based on EU ICSR Implementation Guide document, ***I.C.3.4 Use of local Language in Reaction/Event section and Case Summary section.***

4.2 Literature article submission to SÚKL

In accordance with GVP Module VI, SÚKL can ask the MAH which transmitted to EudraVigilance the initial ADR report originated from scientific literature (where the occurrence country or the primary source country is the Czech Republic) to provide a copy of the source literature article if this provision is not in conflict with copyrights.

For ICSRs in the new E2B(R3) format there are two possibilities to send literature articles. Firstly, it is possible to attach the article to the ICSR itself and send it as an amendment report to EV; SÚKL will obtain the article via rerouting of the ICSR by EMA. The second possibility is to send the article via e-mail in pdf format to e-mail address: farmakovigilance@sukl.cz, where the file name is identical to the ICSR worldwide unique number.

For ICRSs in E2B (R2) format the literature article should only be sent to SÚKL via e-mail to e-mail address: farmakovigilance@sukl.cz in pdf format where the file name is identical to the ICSR worldwide unique number. The articles should be sent in Czech, Slovak or English language.

4.3 Follow-up request

MAHs' follow-up (FU) requests to the reports which have been sent to EV system by SÚKL have to be always substantiated, SÚKL with reference to the GVP Module VI will not accept routine FU requests.
The following situations are covered in as reasons for FU process initiating:

- important additional information is necessary for case evaluation or reconciliation,
- clarifications are needed regarding inconsistent data within ICSRs,
- there is a need to obtain further information in the context of the validation of a signal, the evaluation of a safety issue and so on.

The FU request is to be sent by e-mail to the e-mail address farmakovigilance@sukl.cz

The request has to contain worldwide unique case identification number of the report which is going to be followed-up; it has to be sent in the form of clearly formulated questions; it must not contain repeated questions on facts which have already been stated by the reporter in the ICSR. In case SÚKL obtains the requested information from the reporter, follow-up is processed by SÚKL and the ICSR is sent to EV database only. The e-mail with FU information to the case provided by the reporter is going to be sent to the MAH which requested the FU, SÚKL will not re-send the relevant ICSR to the FU applier as the submitted FU is available for MAH from EVDAS.

On the other hand, MAH could be asked by SÚKL to follow-up the ICSR which has been sent to EV database by the MAH, in reasonable cases described above. For that purpose, SÚKL will contact MAH's contact person for pharmacovigilance issues. The elaborated FU is submitted directly to the EV database by the MAH, FU is going to be re-routed to SÚKL by EMA afterwards.