PHV-4 Version 6 ELECTRONIC REPORTING OF ADVERSE DRUG REACTIONS

As of 5 December 2017, this Guideline shall supersede PHV-4 version 5.

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 follow up on the changes and enhancement of EudraVigilance system and new rules for adverse drug reaction (ADR) reporting (centralised ICSR reporting). The following obligations of the MAHs are cancelled by this version of the Guideline PHV-4:
- registration with SÚKL for ICSR electronic interchange
- testing with SÚKL for ICSR electronic interchange
- registration form up-date
- MAH's ICSR submission directly to SÚKL

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 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

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

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) (Rev. 2) 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 version 5 – Reporting adverse reactions to human medicinal products arising from clinical trials

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 52(2) of the Regulation (EC) No. 726/2004
Central ADR database – a SÚKL database integrated with a gateway, capable of a fully automated electronic interchange of reports with all entities registered in the EudraVigilance system (after EV partner registration)
Registration to the EudraVigilance system – an EMA registration procedure necessary for obtaining access to the EudraVigilance system
Sponsor – a natural or legal person who undertakes the responsibility for the commencement, management and, where applicable, funding of a clinical trial
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 in the CIOMS format).

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 **does not resend any ADR reports** received by SÚKL from HCPs or consumers to MAHs. These reports will be available for MAHs in EudraVigilance database in the extent given by EV Access Policy.

At the same time since 22 November 2017 SÚKL **does not accept** any ICSRs sent by MAHs, MAHs are expected to submit the 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 version 6 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 version 5 and by Directive 2001/20/EC (Clinical Trial Directive) as transposed in the national legislation.

On account of the centralised reporting introduction following obligations of the MAHs are cancelled by this Guideline:
- MAH's submission of the ICSRs originated in CZ directly to SÚKL
- registration with SÚKL for ICSR electronic interchange
- testing with SÚKL for ICSR electronic interchange
- registration form up-date

MAH is obliged to provide information to SÚKL on (local) contact person who is responsible for ICSRs submission. Information on the contact person together with their e-mail and phone contact are to be sent to e- mail address farmakovigilance@sukl.cz.

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 the both fields. – in H.5.r.1b and E.i.1.1b fields.
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

The literature article file attachment is expected for literature reports in new E2B (R3) format, the article should be attached directly to the ICSR in new format sent to EV database.

For literature reports in E2B (R2) format the literature articles are submitted by MAHs to EV literature repository and they are not forwarded by EMA to SÚKL.
For that reason, MAHs submit the literature article related to the E2B (R2) ICSR which had been sent to EVPM by MAH and it has been re-routed to SÚKL by EMA in case it is the ICSR from the Czech Republic.
The articles should be sent to e-mail address: farmakovigilance@sukl.cz in a pdf format with the file name identical to the report's worldwide unique number. Articles will be sent in Czech, Slovak, or English language, normally within five days after submitting the report to EVPM (ideally in parallel with the article submission to EV).

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 (local) contact person in the CZ territory or MAH's QPPV as he is mentioned in Art 57 database. 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.