PHV-4 Version 2 ELECTRONIC REPORTING OF ADVERSE DRUG REACTIONS

As of 9 June, 2015, this Guideline shall supersede PHV-4 version 3.

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 between the State Institute for Drug Control (SÚKL) and marketing authorisation holders and/or clinical trial sponsors. 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

XEVMPD – Extended EudraVigilance Medicinal Product Dictionary

ich icsr – indication (a message type in item M.1.1) for electronic adverse reaction report (ICSR)

ich icsrack – indication (a report type in item M.1.1) for electronic Acknowledgment

EDI – Electronic Data Interchange

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

MPRs – Medicinal Product Reports

ICH – International Conference on Harmonization

ID – Identifier in the EudraVigilance system

EEA – European Economic Area

MedDRA – The Medical Dictionary for Regulatory Activities

GVP – Guideline on good pharmacovigilance practices

ADR – adverse drug reaction

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

Directive 2001/20/EC and follow-up guidance: Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module), Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, Revision 2

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).

EMA's EudraVigilance registration rules and technical specifications of the eXtended EudraVigilance Medicinal Product Dictionary (see http://eudravigilance.ema.europa.eu/human/HowToRegister.asp).

SÚKL instruction KLH-21 version 5 – Reporting adverse reactions to human medicinal products arising from clinical trials

MedDRA Points to Consider: Term Selection: ICH-Endorsed Guide for MedDRA Users (based on applicable MedDRA version)

What to do in case of system failure – EMA steps to follow in case of the EV system technical failure, EMA website: http://eudravigilance.ema.europa.eu/human/SystemFailureSteps.asp

In addition to other information, the GVP summarises instructions given by the Commission and the Agency pertaining to the electronic reporting of suspected adverse drug reactions.

Further specifications may be found in appropriate Q&A documents published continuously on the website of the Agency.

For the purposes of electronic ICSR interchange, EMA has developed the EudraVigilance system based on international ICH guidelines and internationally recognised MedDRA medical terminology. An integral part of the EV system is the XEVMPD database which contains necessary up-to-date information about all medicinal products subjected to the electronic reporting obligation. For the proper functioning of the system it is therefore necessary for all MAHs and sponsors using the EV system to comply with their statutory ICSR obligation to provide and continuously update data about all of their medicinal products.

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

(Please refer also to definitions provided in the EDI and GVP rules: Annex 1 Definitions)

EudraVigilance – a database and a system for electronic interchange of reports within the EEA, established and managed by EMA

Gateway – a software tool allowing for secured electronic data transfer in compliance with the ICH standard between two partners; within the EudraVigilance system; each gateway user communicates with the EMA gateway, which then provides the transferred data to other EudraVigilance users

Webtrader – an EMA web software system allowing for the generation and secured transfer of data within the EudraVigilance system also to users without their own gateway

xml – an electronic data format used for the transfer of standardised data (e.g. submission of data to the database); defined as a subset of the SGML data format, with which it is fully compatible

Internationally recognized medical terminology – terminology complying with the ICH M1 standard, i.e. MedDRA

Individual Case Safety Report (ICSR) – a report of suspected adverse drug reaction

Medicinal Product Report – reporting of information about an authorised or tested medicinal product to XEVMPD

Acknowledgement (ACK) – an ichicsrack report in the xml format – a report sent by the recipient of ICSR or Medicinal Product Report to the sender, confirming successful processing of the sent report (code 01) or informing about errors preventing the processing of this report (code 02 or 03)

Report – in the EudraVigilance system, the following three types of reports are recognised: ICSR, Medicinal Product Report and Acknowledgement (ACK); the type of report is defined in item M.1.1 of the message

Message – an electronic xml file which may contain one or more reports of the same type

Backlog – a group of suspected adverse reactions recorded from May 1 2004 which have not been sent to EV in the xml format as yet; the reports are recorded in SÚKL in paper form only (CIOMS)

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

EV partner registration – a SÚKL registration procedure which explicitly identifies the partner for electronic report interchange from SÚKL's end

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

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.

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 in the relevant items (A.1.6 or B.1.8). For the electronic interchange of reports with SÚKL it is necessary to use the identifier **CZSUKL exclusively**, which is linked with the Central ADR database and allows for automatic generation or receipt of ACKs (ichicsrack xml messages). Registered partners use, on their end, the identifier (ID) they have specified in the current version of their registration form (see section 3.3.1). SÚKL will send reports received from healthcare professionals as well as from the patients to this MAH's ID if the report is serious and meets the expedited criteria (and if the MAH holds a marketing authorisation for the suspected medicinal product stated in the report). Having received the report, the MAH has to acknowledge receipt of this message by sending an ACK (according to the Commission's and Agency's instructions).

Detailed requirements for sending reports (excluding CT reports) to the CZSUKL identifier for the transitional period (until full commissioning of the EV database) are as follows:

	07/2012 until the date of commissioning of the EudraVigilance database
All CZ serious reports	**Yes – report to SÚKL within 15 days**
All CZ non-serious reports	**No – do not report to SÚKL or EV db, process into a PSUR, or provide to SÚKL upon request**
Non-EU serious reports	**No – do not report to SÚKL but report directly to the EV db within 15 days, or provide to SÚKL upon request if the medicinal product in question is also authorised in the Czech Republic**

All reports originating in clinical trials are sent directly to the EMA EudraVigilance database. Reports arising, at the same time, from clinical trials and in the Czech Republic are reported to EMA and to SÚKL in parallel electronically.

Detailed rules for reporting from clinical trials are also explained in KLH-21 Version 5.

3.1 Backlog

The provision of §92 of the Pharmaceuticals Act in the wording effective as of 31 December 2007 stipulates that MAHs are obliged to transmit the data from ADR reports electronically according to guidances of European Commission and EMA, with possible exception to this procedure, specified by SÚKL guideline.

The provision of §93a (2) of the Pharmaceuticals Act in the wording effective as of 2 April 2013 stipulates that MAHs are obliged to electronically submit ICSR data to the European database.

The provision of §93a (5) of the Pharmaceuticals Act defines the procedure for the interim period until the date of full commissioning of the EudraVigilance database.

In connection with the mentioned above SÚKL refers to EMA guideline Volume 9A of The Rules Governing Medicinal Products in the European Union, where an electronic ICSR submission in the frame of the retrospective ADR population is imbedded in a section 11.4, this is applied to ADRs which had occurred after the EMA establishment, i.e. from 1995.. This requirement represents the collaborative effort between all involved stakeholders to support European Risk Management Strategy.

The mentioned guideline among others specifies that with regard to newly acceded EU members all serious adverse reaction reports for the period 1 January1995 to 1 May2004 should be provided by MAHs directly to Eudravigilance database. After the date of the Czech Republic accession to the European Union i.e. from 1 May 2004 it is necessary to provide these reports via national competent authority – SÚKL.

In case MAH has not submitted their backlog reports to SUKL yet it is necessary to accomplished the additional electronic submission of all reports which were reported to SUKL from the date of the Czech Republic accession into the European Union (i.e. from 1 May 2004) in non-electronic way (backlog). The electronic submission has to be done:

- **to the CZSUKL identifier (only applicable to reports from the Czech Republic relating to authorised products in the Czech Republic)**
- **or directly to the EMA EudraVigilance database (applicable to reports from third countries relating to authorised products and all reports from clinical trials).**

The procedure for processing of the backlog is as follows: sending in advance an accurate list of backlog reports to el.icsr@sukl.cz; for each report number this list must contain at least the date of their non-electronic submission to SÚKL, preferably also other information necessary for unambiguous identification of the report. Subsequently, a date of electronic submission of such reports to SÚKL will be arranged with the pharmacovigilance staff (do not send the reports earlier, without a pre-arranged date). The obligation to process the backlog in relation to SÚKL only applies to (backlog) reports from the Czech Republic sent to pharmacovigilance department (not CTs).

Full processing of backlogs for all MAHs in the Czech Republic is expected by SÚKL to be completed no later than 1 April 2014; thereafter SÚKL will take legal action against MAHs who will not comply.

3.2 Registration in the EudraVigilance system

Access to the EudraVigilance system is possible only via registration in EMA (for details please refer to http://eudravigilance.ema.europa.eu/human/HowToRegister.asp).

3.3 Commencement of electronic ICSR interchange with SÚKL

3.3.1 EV partner registration

In order to commence electronic ICSR interchange with SÚKL it is necessary to send a formal application for EV partner registration – by e-mail to el.icsr@sukl.cz. It is necessary to attach an MS Excel registration form which is added to this guideline and which is also available at www.sukl.eu in the pharmacovigilance section in both Czech and English version.

To complete the partner registration process it is necessary to send the same form also in paper form (by ordinary mail, or a scanned copy by e-mail). The properly completed form must be signed by the Qualified

Person Responsible for Pharmacovigilance (QPPV) in the case of a MAH, or by a person responsible for ICSR reporting in the case of a CT sponsor, even if electronic report interchange is provided externally by a third party.

With regard to this application SÚKL will register the EV partner and shall initiate the testing phase. The purpose of this registration is to ensure an explicit allocation of identifiers to specific entities (MAHs or clinical trial sponsors) in the EudraVigilance system, and where several EV identifiers (in the production environment

= "live" IDs) exist for a single entity to clearly define which part of the reporting pertains to a specific identifier

(e.g. reporting from studies from the regional centre, receipt of reports by national branches, etc.).

The registration form contains in particular:

- Identification of the applicant (incl. all marketing authorisation numbers of medicinal products or protocol numbers of clinical trials and EudraCT numbers);
- All relevant EV IDs, date of registration in EMA, and the purpose where applicable (where several "live" IDs exist);
- Contact details of responsible persons, incl. contact persons for the solution of problems that might arise in respect of electronic report interchange, and persons responsible for pharmacovigilance

As far as items concerning implementation schedule are concerned, it is recommended to fill-in the expected schedule for individual steps (start of the partner's reporting, what will be reported, start and end dates of backlog submission in case that no backlog has been submitted yet, etc.); the specified dates are indicative only.

In order to preserve full functionality of the electronic report interchange system, any changes to the data provided in the application for EV partner registration (registration form) must be notified to SÚKL electronically using the updated version of the registration form – the form in xls format is to be sent to the email address el.icsr@sukl.cz.

The updated version of the form shall contain a list of all MPs registered by the MAH, not only the newly added MPs. The version of the form shall be identified by increasing the number of the previous version in the filename by one (please refer also to explanation to Annex 1).

3.3.2 Testing phase

The purpose of the testing phase is to verify technical compatibility of the systems for electronic report interchange and to verify the process of generating reports and ACKs.

For each system, the compatibility of format of interchanged data has to be tested both ways. The objective of testing is to check for correct recognition of interchanged data in all items (incl. ACK), to avoid technical problems with electronic report interchange in production environment. If the system uses several IDs, it is necessary to carry out testing with all of them.

MAHs and sponsors who jointly use a single system with a single ID will carry out testing only once. Where a previously registered gateway user substantially amends their system (e.g. migration to a new database system, a new gateway system, etc.), it is necessary, after testing with EMA, if need be, to perform also new testing with SÚKL, taking into account the amended items. In this case the partner shall apply for new testing, specifying the nature of the implemented changes.

The testing phase proper is similar to testing with EMA; partners will be informed about detailed testing requirements upon successful completion of EV partner registration.

3.3.3 Pilot and production phases

This guideline cancels the transitory pilot phase of electronic report interchange with SÚKL. Upon successful completion of the testing phase, the partner shall be transferred directly to production phase. It is therefore no longer needed to send a paper version of the report (CIOMS I) in parallel.

The obligation to send relevant articles for all literature reports remains unchanged. The articles must be sent to farmakovigilance@sukl.cz in a pdf format with the file name identical to the report's unique number. Articles must be sent in Czech, Slovak, or English within two days after sending the report to SÚKL.

When processing reports which are to be forwarded to the European database and were sent to SÚKL by MAHs from the Czech Republic in accordance with §93a (5) of the Pharmaceuticals Act in the wording effective as of 2 April 2013, SÚKL shall apply all the rules for processing and quality assessment as specified in GVP Module VI. Any identified shortcomings will be resolved immediately with the relevant sender, or taking of remedial measures will be requested, if necessary. Reports not complying with criteria for forwarding to the European database will not be forwarded to EudraVigilance. Any identified shortcoming may be advised to EMA and regulatory authorities of the EEA countries.

3.3.4 SÚKL reports for MAHs

Until the EudraVigilance system is put in operation (that is during the transitional period), any serious reports fulfilling the expedited criteria sent to SÚKL by healthcare professionals and patients will be for forwarded to MAHs holding the marketing authorisation for the suspect medicinal product as they have been so far (within 15 days from the date of receipt). The preferred method of forwarding will be sending electronically to the ID of the MAH holding the marketing authorisation for the suspect medicinal product. As acknowledgment of the receipt of the electronic report, SÚKL requires sending back of ACK in the prescribed format in accordance with rules within two workdays.

MAHs who are temporarily unable to receive reports from SÚKL electronically will be sent reports via an alternative channel, preferably by e-mail; SÚKL database report attached as pdf or rtf file will be sent to a previously agreed general company's e-mail address or to the company's Data Box (Datová schránka). In case of reports forwarded outside the EudraVigilance system (e.g. by e-mail), SÚKL requires the recipient to confirm receipt in writing – by sending an e-mail to el.icsr@sukl.cz.

Forwarded report will be assigned to a globally unique report number under which the report was sent to EudraVigilance. Pursuant to the Commission and Agency guidance, this number must not be replaced with another one and must be used in subsequent report interchange.

If the MAH does not have any other data relevant to the concerned report (follow-up related to parallel receipt of report from a healthcare professional), this report shall not be sent back to SÚKL.

3.4 Provisions governing the method of meeting some statutory obligations

In the case of pharmacovigilance reports from third countries, the obligation to report ICSR shall be deemed met if the report is sent to the EudraVigilance database in EMA.

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 national legislation.

3.5 Exceptions

Exceptions when electronic reporting of ICSR to SÚKL is not required (alternative methods, e.g. CIOMS form, web-based form on SÚKL website can be used):

- In the case of spontaneous reports by healthcare professionals directly to SÚKL (not applicable to the submission of the report by the MAH to SÚKL).
- In the case of reports arising from clinical trials pursuant to S.14(8) of Decree No. 226/2008 Coll. exceptions are granted by the clinical trials department for each study individually based on agreement with the department staff (applies to not-for-profit sponsors of clinical trials – e.g. university studies)
- In accordance with EMA rules for ICSR relating to medicinal products belonging to the category of traditional herbal medicinal products (teas) and homeopathic medicinal products electronic submission of ICSRs related to these products is not required by SÚKL. Eventual reports will be submitted to SÚKL by the holder of marketing authorisation in non-electronic way ensuring compliance with all other legal requirements.
- In case of a technical failure on part of any of the EV partners, both Agency and SÚKL guidelines must be followed: (e-Transmission of ICSRs to the EMA: Steps to follow in case of system failure, available on

https://eudravigilance.ema.europa.eu/human/docs/Guidance/Key%20steps%20to%20follow%20in%20case%20of%20System%20Failure.pdf

and SÚKL guideline „"What to do in case of system failure*" from March* 19 2014, published on SÚKL website SÚKL: in section Medicines /Pharmacovigilance /Documents for pharmacovigilance branch /Guidelines and forms /*What to do in case of system failure?*. This guidance is available on http://www.sukl.eu/medicines/jak-postupovat-pri-technickem-vypadku-na-strane-sukl)

The previously granted exception from electronic reporting is hereby cancelled.

3.6 Rules and time limits for sending Acknowledgements

The EDI rules shall be binding for the electronic interchange of reports (Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs)), incl. time limits for the sending of ACK. With respect to these limits it is advisable to send electronic reports well in advance so that reporting is consistent with the definition of submission of an electronic report. If the sender does not receive an ACK before the expiry of the time limit stipulated by the Act (15 days), they have to consider the report unsent and must employ an alternative solution to meet their statutory obligation.

Annex 1

The electronic version of the MS Excel form for EudraVigilance partner registration for electronic ICSR interchange in the Czech version (Reg-Company-C01.xls) and English version (Reg-Company-E01.xls). The word "Company" in the name of the submitted file has to be replaced with the indication of the registering company. When sending the updated version of the registration form, please replace "01" with the version sequence number (1st update of the registration form after registration has been completed shall be version "02", etc.; "00" may be used for an unofficial version of the form sent together with any potential question if you need a more detailed explanation concerning the completion of items in the registration form).