PHV- 4 version 1 ELECTRONIC ADVERSE DRUG REACTION REPORTING

This guideline supersedes guideline PHV 4 as of September 16 2008.

1. Introduction and general provisions

1.1 Purpose of the guideline

The guideline specifies the rules governing electronic interchange of individual case safety reports (ICSRs) for human pharmaceuticals via the EudraVigilance (EV) system between SÚKL and marketing authorisation holders or sponsors of clinical trials. 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 used abbreviations

SÚKL – State Institute for Drug Control
EMEA – European Medicines Agency, hereinafter also referred to as the "Agency"
EV – EudraVigilance
CT – clinical trial
EV MPD – EudraVigilance Medicinal Product Dictionary
ichicsr – indication (report type in item M.1.1) of electronic ICSR
ichicsrack – indication (report type in item M.1.1) of electronic Acknowledgement
EDI - Electronic Data Interchange
ICSRs – Individual Case Safety Reports
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
ADR – adverse drug reactions

1.3 Legislative and standardisation base of the guideline

- Act No 378/2007 Coll., on Pharmaceuticals and Amendments to Some Related Acts (Act on Pharmaceuticals), as amended, hereinafter referred to as the *Act*
- Decree No 226/2008 Coll., on good clinical practice and detailed conditions of clinical trials on medicinal products and Decree No 228/2008 Coll., on the marketing authorisation of medicinal products
- Directive No 2001/20/EC and related 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
- Volume 10 of The Rules Governing Medicinal Products in the European Union (Clinical trials guidelines)
- 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
- Volume 9A of The Rules Governing Medicinal Products in the European Union **–** Guidelines on Pharmacovigilance for Medicinal Products for Human Use, incl. other EU guidance specified in Appendix 3 (in particular 3.1.1 *EDI rules* and 3.1.2 *EV technical documentation*) and ICH standards provided in Appendix 4 (in particular E2B, M1 and M2)
- EMEA rules governing registration in EudraVigilance and technical specifications of the EudraVigilance Medicinal Product Dictionary (see http://eudravigilance.emea.europa.eu/human/index.asp)

- SÚKL guideline KLH-21 – Adverse reaction reports arising from clinical trials on medicinal products for human use

Volume 9A besides other summarises guidance published by the Commission and Agency on electronic reporting of suspected adverse reactions. This guidance is referred to by Section 92 of the Act. Likewise, the reporting of adverse events and reactions pursuant to Section 58, paragraph 4 of the Act is governed by Commission and Agency guidance published in Volume 10 and related to Directive No 2001/20/EC. 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, EMEA 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 EV MPD database which should contain 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. More detailed explanation of definitions used in the sphere of electronic report interchange

(Please refer also to definitions provided in the EDI rules and in Volumes 9A and 10)

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

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 EMEA gateway, which then provides the transferred data to other EudraVigilance users

Webtrader – an EMEA web software system allowing for the generation and secured transfer of data within the EudraVigilance system as well as 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 authorised or tested medicinal product to EV MPD

Acknowledgement – a report sent by the recipient of ICSR or Medicinal Product Report to the sender, confirming successful processing of the initial 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; 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 one 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

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 EMEA 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 – 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 EMEA 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 report posting 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 (ichicsrack message in the xml format) from the recipient to the sender. The format of the Acknowledgement is also defined by the ICH M2 guideline. Electronic report posting (see Section 92, paragraphs 1 to 6 and Section 58, paragraph 4 of the Act) shall be effective only if the sender of the message or report receives an Acknowledgement 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 always use the identifier CZSUKL, which is linked with the SÚKL ADR database and allows for automatic generation or receipt of Acknowledgments (ichicsrack xml messages). The registered partners use, on their end, the identifier they have specified in the current version of the registration form (see section 3.3.1). SÚKL will send to this Identifier reports pursuant to Section 93, paragraph 2 of the Act. In such a case the MAH has to acknowledge the receipt of this message by means of Acknowledgement (ichicsrack xml message).

All reports originating in the Czech Republic as well as reports referred to in Annex 6 to Volume 9A shall be sent to the identifier CZSUKL (see Section 92, paragraphs 1 to 6 and Section 58, paragraph 4 of the Act). Reports from third countries and all reports arising from clinical trials shall be reported to the EudraVigilance database in EMEA in compliance with the rules specified in Volumes 9A and 10; detailed rules governing reporting from clinical trials are also explained in the KLH-21 guideline. Reports arising, at the same time, from clinical trials and in the Czech Republic, shall be therefore reported in parallel to SÚKL and to EMEA.

3.1 Backlog

With regard to the statutory obligation to enter ICSR data to the European database as of May 1 2004 SÚKL requires that all reports submitted to SÚKL since this date (so called backlog, please refer also to EV partner registration) be electronically sent to SÚKL ex post (this applies to reports concerning authorised products from the Czech Republic (please refer also to Volume 9A, chapter III.11.4) or directly to the EudraVigilance database in EMEA (this applies to reports concerning authorised products from third countries and all reports arising from clinical trials).

When submitting backlog from the Czech Republic to SÚKL, item M.1.1 will remain populated with the text “ichicsr”.

3.2 Registration in the EudraVigilance system

Access to the EudraVigilance system is possible only via registration in EMEA (for details please refer to http://eudravigilance.emea.europa.eu/human/index.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 in hard copy as well as electronically. For this purpose it is necessary to use an MS Excel registration form which forms part of this guideline and which is also available from www.sukl.cz in the pharmacovigilance section both as the Czech and English versions. The paper version of the form must be signed by the statutory representative of the MAH or sponsor responsible for safeguarding ICSRs in compliance with the Act, incl. instances where a change to the contractor in contracted-out electronic ICSR interchange is concerned. 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 third countries from the centre, reporting from studies from the regional centre, receipt of reports by national branches, etc.).

The application for EV partner registration must contain, in particular:

- Identification of the applicant (incl. all marketing authorisation numbers of medicinal products or protocol numbers of clinical trials, or EudraCT numbers where applicable);
- All relevant EV IDs, date of registration in EMEA, and 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;
- Schedule (start of the partner's reporting, what will be reported, due dates for reporting to EV MPD, start and end dates of backlog submission, start date for the receipt of reports from SÚKL).

Any changes to the data provided in the application for EV partner registration must be notified to SÚKL electronically using the updated version of the registration form to the email address el.icsr@sukl.cz, so that full functionality of the electronic report interchange system may be maintained. 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. 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. Acknowledgments), to prevent 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. switches to a new version of EV Technical Documentation), it is necessary, after testing with EMEA, 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 EMEA; partners will be informed about detailed testing requirements upon successful completion of EV partner registration.

3.3.3 Pilot phase

As part of verification of the quality of contents (particularly for items where information may be entered in several ways), a transitory pilot phase will run for each newly registered EV partner who wishes to report to the pharmacovigilance department; in the course of the pilot phase the reporting entity will regularly send electronic as well as non-electronic reports (please see also chapter 3 Method and particulars of reporting). For parallel submission it is essential to send both forms of reports at one time, with the maximum interval of 2 days. The number specified in the non-electronic report must be identical to the globally unique number of the electronic report.

The duration of the transitory phase depends on the amount and quality of the sent reports. The termination of the pilot phase and switch-over to standard electronic report interchange will be announced by SÚKL via e-mail (to the person responsible for electronic reporting and person responsible for pharmacovigilance specified in the application for EV partner registration).

For the purposes of pilot phase it is also possible to avail of reports sent to SÚKL in non-electronic form after May 1 2004; in this case it is necessary to provide an accurate list of reports containing at least the date of submission of the non-electronic reports as well as other data that may

be necessary for a clear identification of the report. This is applicable only to reports from the Czech Republic sent to the pharmacovigilance department.

In any case, pilot phase for entities who fail to electronically send all reports from the Czech Republic after May 1 2004 will not be completed. At the same time, it is necessary to agree upon a binding due date for provision of complete (up-to-date) information to EV MPD (unless this has been done before) and to clear the backlog with EMEA for reports from third countries.

With regard to the obligation to report everything also directly to EMEA, **the pilot phase shall not apply to reports arising from clinical trials**. For EV partners who wish to report only to the clinical trials department, pilot phase is not anticipated. Nevertheless, these EV partners have to devise with SÚKL the clearance of backlog and a due date for submitting all information to EV MPD.

In the case of an agreed common procedure of the EU Member States to ensure the quality of contents of data in the EudraVigilance system, SÚKL reserves the right to adjust rules governing the pilot phase so that it is consistent with the agreed principles. It is, moreover, anticipated that any identified shortcomings will be provided to EMEA and to the regulatory authorities of the EEA countries.

3.3.4 SÚKL reports for MAHs

In order to safeguard the obligations referred to in Section 93, paragraph 2 of the Act, MAHs are obliged to arrange for electronic receipt of reports, including the sending of Acknowledgements in compliance with EDI rules. MAHs who are temporarily unable to receive reports electronically, will be provided with reports via an alternative channel (by fax) with the notification of the globally unique report number under which the report has been sent to the EudraVigilance database. 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 to SÚKL.

3.4 Provisions governing the method of meeting some statutory obligations

For reporting from third countries to the pharmacovigilance department the obligation to submit ICSRs shall be considered satisfied if the report is sent to the EudraVigilance database in EMEA, except for reports where the Czech Republic is the Reference Member State in the MRP for the suspected product (Appendix 6.1 to volume 9A refers). In this case, all reports are to be sent to SÚKL, i.e. reports arising also within the territory of other EEA Member States (reports shall be sent in parallel with submission to the concerned Member State). Rules applicable to reports arising from clinical trials shall be governed by guideline KLH-21 and Volume 10.

3.5 Exceptions:

Cases which do not require electronic submission of reports (the report may be submitted in an alternative way, e.g. using the CIOMS form):

- In the case of spontaneous reports by healthcare professionals directly to SÚKL (not applicable to the hand-over of the report by the MAH).
- In the case of reports arising from clinical trials pursuant to Section 14, paragraph 8 of Decree No 226/2008 Coll. – this has to be arranged for with the clinical trials department for each study.
- In exceptional and duly justified cases referred to in chapter 3.7.
- In case of failure of the EudraVigilance system (see EDI rules); the obligation to send the report electronically after the operation of the system is resumed, however, shall not be prejudiced hereby.

3.6 Rules and time limits for sending Acknowledgements

The EDI rules shall be binding for the electronic interchange of reports, incl. time limits for the sending of Acknowledgements.

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 Acknowledgement before the expiry of the time limit stipulated by the Act, they have to employ an alternative solution to meet their statutory obligation.

3.7 Conditions governing non-electronic ICSRs reported by MAHs

Pursuant to Section 92, paragraph 1 of the Act on Pharmaceuticals, SÚKL may allow for non-electronic ICSR submission if applied for by the MAH. The application must include a rationale thereof, a list of all authorised products, incl. marketing authorisation numbers and marketing authorisation periods, and an overview of adverse reactions for all authorised products for the last five years.

MAHs must meet the following conditions:

- All authorised medicinal products of this MAH are authorised **solely** in the Czech Republic. Cases of reports occurring outside the territory of the Czech Republic which are, pursuant to the effective Commission and Agency rules, to be reported by the MAH to the concerned EEA country or directly to the EudraVigilance database (cases from third countries) are therefore precluded. If these products are authorised in another EEA country, an exemption may be granted if a similar exemption is granted in this Member State (in this case the application must contain also a declaration of potentially granted exemption, incl. the contact person in the regulatory authority responsible for granting the exemption).
- The number of ICSRs per all authorised products for the previous period (five years, if the average period of marketing authorisation of these products is not shorter; in such a case the average will be calculated for the corresponding shorter period) did not exceed 2 reports per year on average. Where a substantial increase in the number of ICSRs per year occurs (e.g. repeatedly more than 5 reports per year), SÚKL reserves the right to terminate the exemption.

The MAH shall, furthermore, ensure that information about authorised products is sent to the EV MPD in compliance with EMEA requirements and cooperate in any potential backlog clearance.

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-C01.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).