KLH-21 version 7

Reporting Adverse Reactions to Medicinal Products for Human Use in a Clinical Trial and to Medicinal Products without Marketing Authorisation

The guideline is being issued on the basis and in compliance with the provisions of Section 56, point 13) Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts, as amended (hereinafter referred to as the "Act on Pharmaceuticals")

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With effect from the date of issue, this guideline supersedes guideline KLH-21, version 6.

This guideline defines the procedure for reporting suspected unexpected serious adverse reactions ("SUSAR") to medicinal products used in clinical trials reported/permitted pursuant to Section 55(4) and (5) of Act No. 378/2007 Coll. on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended. The guideline is intended for the sponsors, investigators and persons cooperating with them within the clinical trial, for holders of registration decisions, if they participate in implementation of clinical trials. The purpose of prompt reports of suspected serious unexpected adverse reactions in clinical trials is to feed new and important information into the pharmacovigilance system of clinical trials that ensures timely identification of signals, which can represent a health risk to the included subjects or possibly may result in a change of the safety profile of the investigational medicinal product (the risk outweighs the potential benefit).

The functional pharmacovigilance system also allows for evaluating identified serious signals and, if necessary, for taking measures to minimise the risk associated with the use of the investigational medicinal products for the subjects participating in the trial, including ensuring that all the parties involved (sponsors, investigators, participating subjects, regulatory bodies and members of ethics committees) are informed in timely manner. The guideline defines the "reporting obligation" of all those who are involved in the system, the scope of such obligations and the manner of performing such obligations (see the overview table at the end of this guideline).

The requirements for reporting adverse reactions are based on

- Act No. 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended ("Act on Pharmaceuticals")
- the applicable implementing provisions for this Act: Decree No. 226/2008 Coll., on good clinical practice and detailed conditions of clinical trials on medicinal products ("Decree on GCP") and Decree No. 228/2008 Coll., on marketing authorisation of medicinal products
- the guideline of the International Conference on Harmonisation E6 on Good Clinical Practice, issued by the European Medicines Agency (EMA) as guideline CPMP/ICH/135/95 (International Conference on Harmonisation – E 6 – Good Clinical Practice: Consolidated Guideline)
- the guidelines of the European Medicines Agency (EMA) and European Commission, issued according to Directive 2001/20/EC (Guidelines on good pharmacovigilance practices (GVP); Volume 10 – Clinical trials guidelines – Chapter II: Safety Reporting; Communication from the Commission: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ("CT-3"), June 2011; ICH guideline E2F, Note for guidance on development safety update reports, September 2010

Abbreviations used:

SUKL – State Institute for Drug Control

EC – ethics committee

LEC – local ethics committee

MEC – ethics committee for multicentric trials

MP – medicinal products

investigational MP = meaning the tested MP or comparator MP (see the definition of the Act on Pharmaceuticals, Section 51(2)(c))

CT – clinical trial

IB – investigator´s brochure = set of information for the investigator

SmPC – summary of product characteristics

PhV - pharmacovigilance

GIT – gastrointestinal tract

MAH – Marketing Authorisation Holder

TS – trial subject

CRO – ontract research organisation f

RSI – Reference Safety Information

AE – Adverse Event

AR – Adverse Reaction

SAE – Serious Adverse Event

SAR – Serious Adverse Reaction

SUSAR - Suspected Unexpected Serious Adverse Reaction

DSUR – Development Safety Update Report

DS – Data Box

DSMB - Data Safety Monitoring Board

MedDRA - Medical Dictionary for Regulatory Activities

I. DEFINITION OF TERMS USED IN PHARMACOVIGILANCE

Adverse Event (abbreviated as **AE**) means an adverse change in the health condition affecting the patient or the trial subject who is the recipient of the medicinal product, even if it is not known whether it is in causal relationship with the treatment with this medicinal product. (Section 3(5) of the Act on Pharmaceuticals)

Thus, an adverse event can be any adverse and undesired manifestation (including, for example, a deviation of laboratory results), a symptom or an illness taking place concurrently with the use of the medicinal product, regardless whether it is deemed that it is related to the medicinal product or not.

The term "adverse event" summarily designates all the situations, in which an adverse change of health condition occurs. It is used only until it is possible to state at least a suspicion that the given adverse change of health condition might have been caused by the administration of a specific medicinal product or products (including placebo). Since such suspicion cannot be stated particularly under the conditions of a blind clinical trial (the investigator does not know what the patient uses), the term "adverse event" is by far most often used in a clinical trial.

Adverse Drug Reaction (abbreviated as **ADR**) – means a reaction to a medicinal product, which is adverse and unintended. (Section 3(4) of the Act on Pharmaceuticals)

With respect to investigational medicinal products, the definition also includes errors in medication and the methods of using not stated in the protocol, including incorrect use or abuse of the medicinal product, regardless of the dose of the medicinal product. The definition implies reasonable probability that there is a causal relationship between the event and the investigational medicinal product. This means there are facts (evidence) or arguments indicating a causal relationship.

Adverse reaction is a term, which implies a certain degree of causality. In a clinical trial, it is an adverse event, in the case of which it is possible to state suspicion of a causal relationship with a certain medicinal product or multiple medicinal products, which were used in the study. In a blinded clinical trial, it is possible to use the term "adverse reaction" only after the case is unblinded.

Serious Adverse Event (abbreviated as **SAE**) - means such adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in permanent or significant damage to health or limitation of capabilities or is manifested as a congenital anomaly or birth defect in offspring, irrespective of the administered dose of the medicinal product (Section 3(6) of the Act on Pharmaceuticals).

These characteristics/after-effects need to be taken into account when the event occurs. For example, in the case of a life-threatening event, it is an event where the life of the subject was threatened at the time when the event occurred; thus, it is not an event that could have hypothetically caused death, if its course was more serious. Some health events may threaten the subject or may require an intervention that will prevent occurrence of one of the aforementioned characteristics or one of the aforementioned after-effects. These events ("Significant Health Events") should also be regarded as "serious" in accordance with the definition. The decision on whether a specific event is "serious" according to these criteria needs to be made based on medical and scientific judgement.

Serious Adverse Drug Reaction (SADR) means such adverse drug reaction which results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in permanent or significant damage to health or limitation of capabilities or is manifested as a birth defect in offspring. (Section 3(4)(a) of the Act on Pharmaceuticals)

Unexpected Adverse Drug Reaction means such adverse reaction the nature, severity or consequence of which is not consistent with the information available, for example with the investigator's brochure for an investigational medicinal product without marketing authorisation, or with the summary of product characteristics for an authorised medicinal product. (Section 3(4)(b) of the Act on Pharmaceuticals)

Unexpected events are presented in reports that provide significant additions to the existing information on a known, already documented serious adverse reaction as concerns the specificity, increase of its incidence or seriousness.

Expectedness of an adverse reaction is determined by the sponsor in the Reference Safety Information (RSI). This should be done according to previously observed events and not according to what can be expected according to the pharmacological properties of the given medicinal product. RSI is stated in the summary of product characteristics or in the investigator's brochure (the guidelines regards RSI are elaborated on in greater detail in Section 7.2.3.2 of the European Commission's Guideline CT-3).

Unexpected Serious Adverse Reaction must comply with the definition of a serious adverse reaction and, at the same time, that of an unexpected adverse reaction.

Suspected Unexpected Serious Adverse Reaction (abbreviated as **SUSAR**) – occurrence of serious unexpected adverse reaction is in causal relationship with the investigational medicinal product. Evaluation of whether there is reasonable probability of a causal relationship is usually carried out by the investigator. If the investigator presenting the report does not provide information on a causal relationship, the sponsor should contact the investigator and request the investigator to comment on this aspect. The evaluation of the causal relationship provided by the investigator should not be taken lightly by the sponsor. If the sponsor does not agree with the result of the evaluation of the causal relationship provided by the investigator, the report should contain both the opinion of the investigator and the opinion of the sponsor.

II. LEGISLATIVE REQUIREMENTS GOVERNING REPORTING IN THE COURSE OF CLINICAL TRIALS

1. Obligations of the Investigator

- The investigator is obliged to promptly report all serious adverse events (SAEs) to the sponsor, except for those which are defined in the Protocol or the investigator's brochure as events not requiring prompt report. A prompt report will be followed be detailed written reports. In prompt and follow-up reports, subjects are identified using unique numerical codes, which were assigned to the subjects. It is necessary to state the identification of the clinical trial, preferably the EudraCT number, in the report.
Note: Promptly means no later than within 24 hours from the moment when the investigator has learnt about the fact.

- The investigator will report adverse events and/or laboratory deviations, defined by the Protocol, to the sponsor according to the reporting requirements and within the time limits set in the Protocol.

- In the event of death of a trial subject, the investigator is obliged to provide the sponsor and the ethics committee (MEC and the relevant LEC) with the requested additional information.

2. Obligations of the Sponsor

The sponsor will be fully responsible for the conduct of the clinical trial and for the safety of the subjects participating in the clinical trial. The following obligations of the sponsor are associated with the aim to safeguard the safety of trial subjects:

- The sponsor will be obliged to ensure that any information on suspected unexpected serious adverse reactions resulting in death of or life-threatening for the trial subject is recorded and reported to SUKL (via EudraVigilance database) and to the ethics committees concerned without any delay, no later, however, than within 7 days of the day when the sponsor has learnt about this fact, and that any subsequent additional information, if necessary, is provided within the next 8 days. If all the necessary information is contained in the initial report, it is not necessary to provide a follow-up report.
- In the case of other suspected unexpected serious adverse reactions the sponsor shall ensure that a report thereof is given to SUKL (via EudraVigilance database) and to the ethics committees concerned no later than within 15 days of the day when the sponsor has learnt about this fact.
- *Note:SUSAR report will be given **only** electronically; the sponsor should report SUSAR directly to the EudraVigilance database to EVCTM module. Those sponsors who do not have access to the electronic exchange of SUSARs with the EudraVigilance database and SUKL – i.e. particularly the sponsors of grant clinical trials not backed by pharmaceutical companies, i.e. the grant studies presented by physicians or professional societies, can request SUKL in a written request to make input into the EudraVigilance database on their behalf. After the request is processed, SUSARs are to be sent to SUKL using an electronic form available on the SUKL website (http://www.sukl.cz/nahlasit-nezadouci-ucinek). It is necessary to enter the note "From a clinical trial" in the comment box and to state the EudraCT number and the abbreviated name of the study for identification. Without these 2 pieces of information, SUKL cannot report the SUSAR on behalf of the sponsor. This option does not concern the sponsors backed by pharmaceutical companies.*
- The sponsor should inform the investigators of any suspected unexpected serious adverse reactions to the investigational MP known to the sponsor.
- The sponsor should maintain detailed records of all adverse events reported to the sponsor by the investigator(s). Upon request the sponsor shall provide these records to SUKL (Section 58(3) of the Act on Pharmaceuticals); the sponsor will also provide these records upon request to the competent authorities of the Member States on whose territories the clinical trial is also taking place (Section 58(3) of the Act on Pharmaceuticals).
- The sponsor should, on an annual basis or upon request, submit to SUKL and to the ethics committee (to the MEC where multicentre CTs are concerned, or to the LEC which has approved the trial where single-centre CTs are concerned) the **development safety update report (DSUR)**, which reflects any new information which is available and which has been obtained during the period which the report pertains to. This report will be identical for SUKL as well as for the EC (the MEC where multicentre CTs are concerned, or the LEC where single-centre CTs are concerned) in the structure and scope defined by the ICH Guideline E2F, Note for Guidance on Development Safety Update Reports, September 2010. DSUR will be submitted for the CTs taking place in the Czech Republic (for the period from the beginning of a CT to its end, with the end of a clinical trial being defined by the protocol of the CT, DSUR covering this period must be submitted to SUKL)*.*
- In the course of a clinical trial, the sponsor shall provide SUKL and the ethics committee (the MEC where multicentre CTs are concerned, or the LEC which has approved the trial where single-centre CTs are concerned) with **the annual report on the course of the clinical trial** every 12 months, no later than within 60 days from the end of this period (this period will start at the commencement of the CT in the Czech Republic) (Section 58(8) of the Act on Pharmaceuticals; Section 15(3) of the Decree on GCP) in the scope set forth in Annex 6 to the Decree on Good Clinical Practice.

3. Information to be sent to SUKL, to the ethics committees concerned and to the investigators involved in the given clinical trial if the clinical trial is suspended or terminated in the Czech Republic:

*Where the conduct of a clinical trial is suspended in the Czech Republic, **Annual Safety Reports** should be sent in compliance with the original timelines.*

In the case of a terminated clinical trial in the Czech Republic the sponsor will promptly provide the information; in cases, in which the information contains unexpected safety information, it should be accompanied by proposed measures to be adopted, if the information significantly alters the risk-benefit ratio and may affect trial subjects involved in the terminated trial. After the clinical trial is terminated in the Czech Republic, the Annual Safety Reports will no longer be submitted, even if the clinical trial continues abroad.

III. RECORDING, EVALUATING AND REPORTING ADVERSE EVENTS AND ADVERSE REACTIONS

The sponsor will be responsible for establishing a system for recording, collecting data on, evaluating, saving and reporting all types of AEs and ADRs by creating standard operating procedures which have to be executed in writing.

The sponsor will evaluate the records of all **adverse events** in terms of their severity and causality (*in compliance with the above definitions*).

Any **adverse events** considered by the investigator or the sponsor as being suspect of causal relationship with the investigational MP will be classified as **adverse reactions.** The evaluation of causality by the investigator must not be disputed by the sponsor; if the sponsor does not agree with the investigator's evaluation of causality, both opinions have to be stated in the report.

The expectedness of adverse reactions must be defined by the sponsor in the Protocol and RSI (IB or SPC) with regard to the available information on the product. Where there are different SPCs for the same investigational MP in various countries, the sponsor will choose one SPC (specified in the Protocol) as the reference one and expectedness will be established on the basis thereof. When **unexpectedness of an adverse reaction** is evaluated, the aim is to evaluate inconsistency with the information provided in the IB, Protocol or SPC in respect of the nature, severity and frequency of occurrence (rare vs. common), or consequence (see the definition of UADR above).

1. WHAT TO REPORT AND TO WHOM TO REPORT

1.1 Reporting To SUKL – to be reported by the **sponsor**

Sponsor reports to SUKL via direct reporting to EudraVigilance, EVCTM Module only **SUSARs**, i.e. suspect cases derived from **unblinded** data; a reaction is a SUSAR when both seriousness and unexpectedness are simultaneously present; adverse reactions, which are stated in RSI are not unexpected and hence are not SUSARs. Reports, which are not reports on SUSARs, are a part of DSUR.

IMMEDIATELY

- **SUSAR** to an investigational MP which resulted in death or was life-threatening for TS is to be reported**within 7 days + a follow-up report is to be submitted within the next 8 days** (if all the information was provided in the primary report, no follow-up report is to be submitted).
- **other SUSARs** (i.e. those that did not result in death or were not life-threatening) **are to be reported within 15 days.**
- Any changes increasing the risk to trial subjects and new information which may adversely affect the safety of trial subjects or the conduct of the clinical trial will be reported promptly, within time limits reflecting the assumed degree of significance of the information and the risk for patients.

OTHER REPORTING

- **DSUR** – the sponsor will submit the development safety update report which reflects any newly available information obtained in the course of the period which the report pertains to once a year. The contents of the report will be governed the ICH Guideline E2F, Note for Guidance on Development Safety Update Reports, September 2010. DSURs are required to be sent only electronically (in the pdf format on a data medium by mail or by e-mail to klinsekret@sukl.cz with identification of the clinical trial).
- **Updated version of the IB –** at least once a year (Section 56(4) of the Act on Pharmaceuticals).
- **Information on the death of any subject in a CT** in the Czech Republic – within 7 days in the form of a cover letter (if the death of the subject complies with the definition of SUSAR, it is, of course, to be reported in the way defined for reporting SUSAR), stating the identification of the clinical trial, the investigating physician and a brief description of the case. If a high mortality rate is assumed in a clinical trial, it is possible to present this information as a part of the annual interim report on the clinical trial based on request for waiver of this obligation, submitted with Request for Authorisation of Clinical Trial.
- Prompt notification of any change increasing the risk to subjects and any new information that can have an adverse impact on the safety of subjects or on the conduct of the clinical trial, including reports on SUSARs from abroad, rated as such (referred to as "Urgent Safety Restriction" or "Urgent Safety Measure").

1.2 Reporting to MEC

Sponsor reports only **SUSARs**, i.e. suspect cases derived from **unblinded** data.

IMMEDIATELY

- **SUSAR to an investigational MP** (with or without marketing authorisation) arising from the clinical trial concerned and occurring within the territory of the Czech Republic, which resulted in death or was life-threatening for TS, is to be reported within 7 days + a follow-up report is to be submitted within the next 8 days (if all the information was provided in the primary report, no follow-up report is to be submitted); other SUSARs that occurred within the territory of the Czech Republic will be reported within 15 days. The sponsor will notify the MEC and LEC in the location where the SUSAR occurred.

  *Note: The sponsor will send individual reports to the **ethics committees**; if possible, in the follow-up stage, these will be supplemented by a brief description containing an evaluation of the assumed causality and the necessary measures, if any, or conversely a rationale explaining why no measures are necessary.*

- The sponsor will promptly report any changes increasing the risk to subjects and any new information that can have an adverse impact on the safety of subjects or on the conduct of the clinical trial, including reports on SUSARs from abroad, rated as such.

OTHER REPORTING

- **"Line listing"** together with a cover letter which includes the evaluation of the safety situation, whether it is necessary to adopt safety measures, and if so, which ones, including their justification. Line listing contains reports on SUSARs for the investigational MP (authorised in the Czech Republic as well as non-authorised in the Czech Republic), arising from the clinical trial conducted within the territory of the Czech Republic, which have occurred in the Czech Republic or abroad (within the territory of the EU or in a third country). It will be sent by the sponsor every 6 months, only to the MEC. Line listing should be sent within the period of 60 days from the date of completion of data collection for the given period.
- **DSUR** – the sponsor will submit a DSUR once a year (for a MEC, it is sufficient to send a DSUR summary, if the MEC does not require submission of a complete DSUR).

1.3 Reporting to LEC

in the location where the CT concerned is conducted – to be reported by the sponsor

The sponsor will notify the LEC in the location where the SUSAR occurred.

IMMEDIATELY

- **SUSAR to an investigational MP** (with or without marketing authorisation in the Czech Republic) arising from the clinical trial concerned and occurring within the territory of the Czech Republic, which resulted in death or was life-threatening for TS, is to be reported within 7 days + a follow-up report is to be submitted within the next 8 days (if all the information was provided in the primary report, no follow-up report is to be submitted); other SUSARs that occurred within the territory of the Czech Republic will be reported within 15 days, unblinded, but without the subject identification number – without the complete subject identification and without identification of the MP The sponsor will inform the MEC and LEC in the location where the SUSAR occurred.

  *Note: The sponsor will send individual reports to the **ethics committees**; if possible, in the follow-up stage, these will be supplemented by a brief description containing an evaluation of the assumed causality and the necessary measures, if any, or conversely a rationale explaining why no measures are necessary.*

- The sponsor will promptly report any changes increasing the risk to subjects and any new information that can have an adverse impact on the safety of subjects or on the conduct of the clinical trial, including reports on SUSARs from abroad, rated as such.

OTHER REPORTS will only be submitted if requested by the LEC concerned.

1.4 Reporting to Investigators – to be reported by the **sponsor**

The sponsor will report **SUSARs**, i.e. suspect cases derived from unblinded data, but without identification of subjects (i.e. without the identification code of the TS), and without information on the MP and/or blinded reports.

- **SUSAR** to an investigational MP (with or without marketing authorisation in the Czech Republic) arising from the clinical trial concerned and occurring within the territory of the Czech Republic is to be reported within 15 days, unblinded, but without the subject identification number – without the complete subject identification and without identification of the MP.

- **SUSAR** to an investigational MP (with or without marketing authorisation in the Czech Republic) arising from the clinical trial concerned and occurring within the territory of the EU or in a third country is to be reported according to the rules set by the sponsor:
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  - either within 15 days, unblinded, but without the subject identification number – without the complete subject identification and without identification of the MP;
  - or the sponsor will send them in the form of "line listing" every 6 months, without the subject identification codes and without the identification of the MP.
- **"Line listing"** - of SUSARs of the tested MP (with or without marketing authorisation in the EU) arising from another clinical trial on the same tested MP conducted within the territory of the Czech Republic, which have occurred within the territory of the Czech Republic, or of SUSARs arising from another clinical trial on the same tested MP conducted within the territory of the Czech Republic, which have occurred within the territory of the EU or in a third country. It will be sent by the sponsor every six months without giving the identification codes of subjects and without the identification of the MP.
- The sponsor will immediately report any changes increasing the risk to subjects and any new information that can have an adverse impact on the safety of subjects or on the conduct of the clinical trial, including reports on SUSARs from abroad, rated as such (for example, in the form of a Dear Investigator Letter).

2. WHAT IS NOT TO BE REPORTED

- serious but expected reactions (i.e. the ones stated in RSI),
- non-serious reactions, irrespective of their expectedness,
- events evaluated as being without causal relationship with the investigational MP (the causality is evaluated by the investigating physician); without evaluation of the causality, the report is not accepted into the EudraVigilance system; for evaluation of causality, the reports need to be unblinded,
- reports that have not been unblinded are not to be sent

3. RECOMMENDATIONS FOR UNBLINDING

The major rule for SUSAR reporting is to unblind the report before submitting it. As it is, however, desirable to maintain blinding for all patients prior to the final analysis, it is recommended that the sponsor only unblinds the particular patient. The sponsor should strive to opt for such method of monitoring and processing of safety data which allows for maintaining the blinding for persons responsible for data analysis and interpretation of results in the conclusions of the study. The unblinding of individual cases by investigators in the course of the study should be conducted exclusively with respect to the subject safety – only in exceptional critical emergency situations and in compliance with the Protocol. The investigator must always have the option to carry out the unblinding in the event of a situation in which the safety of the subject is threatened (in a life-threatening situation where the information on the administrated MP is important for ensuring provision of medical care = safety of the patient).

Where a blinded study is concerned, it is recommended to assess the severity, expectedness and possible causal relationship of the SADR/SAE with the investigational MPs in terms of their potential effects. If, after such assessment, the case appears to be a SUSAR, unblinding is necessary. In this case it is necessary to reconsider, before reporting, the expectedness and the method of reporting implied thereby in respect of the specific medicinal product (tested, comparator vs. authorised, non-authorised vs. information from the Protocol, RSI).

In clinical trials involving diseases with high morbidity and/or mortality rates where the endpoints of the evaluation of efficacy may be fatal or other serious conditions, unblinding would compromise the integrity of the study. That is why it is recommended in such special cases to include a modification of the method of reporting adverse reactions in the Protocol so that serious conditions which may be considered related to the disease would not have to be reported through the system involving the use of an immediately unblinded report. SUKL will approve such modification within the scope of assessment and approval of the Protocol of the CT concerned. However, if an adverse reaction which does not represent an endpoint occurs, it has to be reported in the usual manner. Also, sponsors are advised to establish an independent data and safety monitoring board (DSMB) which would evaluate data at pre-set intervals and which could, based on the results of the safety analysis, give the sponsor recommendations on whether it is possible to continue the CT without any changes, whether measures or changes need to be adopted, or whether the board recommends terminating the study.

4. REPORTING FORMATS

All reports are to be submitted directly to the EudraVigilance database. Only sponsors of non-commercial studies from the Czech Republic that are not supported by any pharmaceutical company or any other commercial organisation may request SUKL to submit a report on their behalf into the EudraVigilance system (based on a written request). After the request is processed, SUSARs are to be sent to SUKL using an electronic form available on the SUKL website (http://www.sukl.cz/nahlasit-nezadouci-ucinek). It is necessary to enter the note "From a clinical trial" in the comment box and to state the EudraCT number and the abbreviated name of the study for identification. Without these 2 pieces of information, SUKL cannot report the SUSAR on behalf of the sponsor.

DSURs are to be sent only in an electronic format (on a medium (CD) or by e-mail to the address klinsekret@sukl.cz, possibly via the secure file transfer system (Eudralink)). Archival zip and rar formats may be used for sending DSURs. For security reasons, SUKL will not accept self-opening archives of the exe or similar formats.

Other safety information that is subject to prompt reporting will be reported by means of a letter as a report pertaining to safety, specifying the EudraCT number, the Protocol number and, if applicable, SUKL file number/identifier of the study, to which the information pertains. The letter should contain brief information about the problem and a proposed solution or a description specifying how the sponsor will proceed in addressing this problem.

5. MINIMUM CONTENT OF THE REPORT

5.1 A report on a serious adverse reaction by the investigator to the sponsor will contain at least the following (Section 10(1) of the Decree)**:** Information on the trial site; Name of the sponsor; Name of the clinical trial and the Protocol number; Patient identification; Description of the event; Names of all the medicinal products taken by the subject, including the administered dose and the method of administration; Evaluation of causality between the AE and the investigational MP. *Note: The above-mentioned requirements reflect the minimum particulars of reporting but in order to make proper evaluation of causality possibly, it is advisable to provide other relevant information, for example, concomitant treatment with other medicinal products or various dietary supplements, which might have been involved in the induced event. Detailed specification of the scope and method of reporting should form a part of the Protocol of any study. It is possible to state the name of the active substance or the code of the pharmaceutical instead of the name of the medicinal product.*

5.2 A report on suspected unexpected serious adverse reaction by the sponsor will contain at least the following: Valid EudraCT number and abbreviated name of the study; Number of the sponsor's study; One identifiable subject with an assigned code; One identifiable person submitting the report; One suspected unexpected serious adverse reaction; One suspected investigational medicinal product (including its name – the code of the active substance); Evaluation of causality.

5.3 Line listing (a list) will bear an identification number, date and time of compilation and will **contain** the following information on each SUSAR, in particular**:** Identification of the clinical trial (Protocol number of EudraCT number); Identification number of the trial subject in the study (*not to be specified if the report is submitted by the investigator*); Case-ID-Number in the sponsor's database; Country in which the case occurred; Age and gender of the trial subject; Daily dose of the investigational medicinal product (and the pharmaceutical form and method of administration, if possible); not to be specified if the report is submitted by the investigator; Date of onset of the AR (if not available, then an estimate based on commencement of the treatment); Duration of the treatment (if not available, then an estimate of the duration of the treatment); Description of the adverse reaction (sings, symptoms, in the MeDRA terminology, if practicable); Evaluation of the final condition of the subject (e.g. improved, recovered, fatal, with consequences…); Evaluation of causality (if investigator's and sponsor's evaluations are diverging, both will be provided) and of expectedness.

Annex 1 – Tabular Overview of Pharmacovigilance Reporting from Clinical Trials

To be reported	To EVCTM	To SUKL	To the ethics committee	To the investigator
A. SUSARs, which resulted in death or threat to life (1-4 below)	7+8 days	NO	7+8 days	within 15 days

B. SUSARs of other severity than A (1-4 below)	within 15 days	NO	within 15 days	within 15 days
1. SUSAR arising from CZ	YES	NO	YES (MEC + LEC in the location)	YES
2. SUSAR arising from EU, outside of the CZ/the CT is conducted in CZ	YES	NO	NOT separately, but as the 6 months line listing	YES **or** as the 6 months line listing
3. SUSAR arising from outside of the EU/the CT is conducted in the EU	YES	NO	NO	YES **or** as the 6 months line listing
4. SUSAR arising from outside of the EU/the CT is conducted outside of the EU *(the sponsor conducts a CT with the same active substance in the EU)*	YES	NO	NO	6 months line listing
C. DSUR	NO	once a year	once a year (as a DSUR summary, only to MEC)	NO
D. line listing	NO	only upon request	every 6 months (only to MEC)	every 6 months
E. other safety information *(immediate notification of any change increasing the risk to subject and any new information that can have an adverse impact on the safety of subjects or on the conduct of the CT, (referred to as "Urgent Safety Restriction" or "Urgent Safety Measure")*	NO	immediately	immediately	immediately

CZ – the Czech Republic