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**Detailed guidance on the collection, verification
and presentation of adverse reaction reports
arising from clinical trials on medicinal products
for human use**

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1. INTRODUCTION

Article 18 of Directive 2001/20/EC¹ requires the Commission in consultation with the European Medicines Agency, Member States and interested parties to draw up and to publish detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions.

According to Article 16(1) and (2) of Directive 2001/20/EC the investigator shall report all serious events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluation shall be reported to the sponsor according to the reporting requirements within the time periods specified in the protocol.

The investigator shall supply according to Article 16(3) of Directive 2001/20/EC the sponsor and the Ethics Committee with any additional requested information, notably for reported deaths of a subject.

According to Article 16(4) of Directive 2001/20/EC the sponsor shall keep detailed records of all adverse events and he shall submit these records on request to the Members States in whose territory the clinical trial is being conducted.

According to Article 17(1)(a) and (b) of Directive 2001/83/EC the sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions have to be recorded and reported to the competent authority of the Member State concerned and the Ethics Committees in defined timelines.

According to Article 17(1)(d) the sponsor has also to inform the investigator.

According to Article 17(2) of Directive 2001/20/EC the sponsor shall provide to the Member States in whose territory the clinical trials is being conducted and the Ethic Committees every year with a listing of all suspected serious adverse reactions which have occurred over this period.

2. SCOPE

This detailed guidance sets out guidance on the collection, verification and presentation and decoding procedures of adverse event/reaction reports arising from clinical trials on medicinal products for human use. In addition, it sets out the responsibilities of the concerned parties.

This guidance applies to all clinical trials on medicinal products for human use within the scope of Directive 2001/20/EC conducted within the European Community (with at least one investigator site in the Community). It applies to all investigational medicinal products for human use independently from their marketing authorisation status in any Member State whether or not investigational medicinal products are used under the conditions of the marketing authorisation.

¹OJ L 121, 1.5.2001 p.24

3. DEFINITIONS

The definitions of Directive 2001/20/EC, Article 2, are applicable. Collection, verification, decoding, presentation and reporting of adverse reactions should be consistent with the adopted Community Guidelines².

4. RESPONSIBILITIES

4.1 Investigator's Responsibilities

With regard to notification of adverse events set out in Article 16 of Directive 2001/20/EC.

4.2 Sponsor's Responsibilities

4.2.1 General Remarks

The sponsor is responsible for the ongoing safety evaluation of the investigational medicinal product(s).

The sponsor is responsible for the prompt notification to all concerned investigator(s), the Ethics Committee and competent authority of each concerned Member State of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC.

The sponsor is responsible for arranging systems and written standard operating procedures to ensure that the necessary quality standards are observed in every step of the case documentation, data collection, validation, evaluation, archiving and reporting.

4.2.2 Recording and Evaluation of Adverse Events (AEs)

Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases.

Individual adverse events should be evaluated by the investigator and where indicated by the guidance in section 5, they should be reported to the sponsor for evaluation. This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

The sponsor must retain detailed records of all adverse events reported to him by the investigator(s) and perform an evaluation with respect to seriousness, causality and expectedness.

On request of a competent authority in whose territory the clinical trial is being conducted, the sponsor should submit detailed records of all adverse events which are reported to him by the relevant investigator(s).

4.2.3 Assessment of seriousness

Seriousness shall be determined according to the definition in Article 2(o) of Directive 2001/20/EC taking into account the comments presented in Annex 1.

² Electronic standards for reporting are identified in EudraLex Volume 9 PART III - EU ELECTRONIC EXCHANGE OF PHARMACOVIGILANCE INFORMATION for details on standards for electronic reporting

4.2.4 Assessment of causality

Causality shall be determined according to the definition of an adverse reaction as given in Article 2(m) of Directive 2001/20/EC taking into account the comments presented in Annex 1.

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both, the opinion of the investigator and the sponsor should be provided with the report.

4.2.5 Sponsor's assessment of expectedness

The definition of the term "unexpected adverse reaction" is given in Article 2(p) of Directive 2001/20/EC taking into account comments in Annex 1. Adverse reactions should be considered as unexpected if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information for the IMP.

The expectedness of an adverse reaction shall be determined by the sponsor according to the reference document³. The reference document is, as a general rule:

- the investigator's brochure for a non authorised investigational medicinal product,
- or the summary of product characteristics for an authorised medicinal product in the European Community, which is being used according to the terms and conditions of the marketing authorisation). When the investigational medicinal products has a marketing authorisation in several Member States with different summary of product characteristics, the sponsor should select the most appropriate summary of product characteristics, with reference to patient safety, as a reference document for assessing expectedness.

The reference document is the same for the whole clinical trial in all the Member States concerned. It should be clearly identified in the protocol and attached to the Clinical Trial Application, in an acceptable language and mentioned in the covering letter.

4.2.6 Data protection of trial subjects

The Community standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed⁴.

5 REPORTING OF SERIOUS ADVERSE REACTIONS

5.1 Standards for expedited reporting

5.1.1 What must be reported?

5.1.1.1 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Tabulation of reporting rules and steps to avoid duplicates are also set out in the 'Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module).

The sponsor of a clinical trial (Phase I-IV) with at least one investigator site in the Community must report SUSARs according to the following scenarios:

³ See also section 4.1.5 of the 'Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities in the European Union, notification of substantial amendments and the declaration of the end of a clinical trial'. <http://pharmacos.eudra.org/F2/pharmacos/dir200120ec.htm>

⁴ Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995, as amended by Regulation (EC) No 1882/2003

a) SUSARs which occur within the concerned trial

All suspected adverse reactions related to an investigational medicinal product (the tested investigational medicinal products and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

b) SUSARs which occur outside the concerned clinical trial

(1) For investigational medicinal products that have a marketing authorisation in a Member State and the sponsor is the marketing authorisation holder:

Where the investigational medicinal product has a marketing authorisation in a Member State, and the sponsor is the marketing authorisation holder, the reporting of SUSARs which occur

(i) outside the concerned clinical trial and outside any other clinical trial (including SUSARs arising from any organised data collection system other than interventional clinical trials) should be in accordance with the Regulation (EC) No. 726/2004, Directive 2001/83/EC and

(ii) if it occurs in a clinical trial according the 'Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)'.

(2) For investigational medicinal products that have a marketing authorisation in a Member State and the sponsor is not the marketing authorisation holder:

Where the investigational medicinal product has a marketing authorisation in any Member State, and the sponsor is not the marketing authorisation holder, any SUSARs associated with the investigational medicinal products that occur in another trial conducted by the same sponsor in a third country should be reported.

(3) For investigational medicinal products that do not have a marketing authorisation in any Member State of the Community:

Where the investigational medicinal product does not have a marketing authorisation in any Member State of the Community, any SUSARs associated with the investigational medicinal products are subject to expedited reporting, as soon as the sponsor becomes aware of them. This includes:

- SUSARs which occur in another trial conducted by the same sponsor either in the Community or in a third country (i.e. in EEA countries),
- or which are identified by spontaneous reports or a publication,
- or which are transmitted to the sponsor by another regulatory authority.

5.1.1.2 Other safety issues requiring expedited reporting

Other safety issues also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial, for instance:

- a) an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important,
- b) post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the sponsor,
- c) new events related to the conduct of the trial or the development of the investigational medicinal products and likely to affect the safety of the subjects, such as:

- a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
 - a significant hazard to the subject population such as lack of efficacy of an investigational medicinal products used for the treatment of a life-threatening disease,
 - a major safety finding from a newly completed animal study (such as carcinogenicity)
 - any anticipated end or temporally halt of a trial for safety reasons and conducted with the same investigational medicinal products in another country by the same sponsor,
- d) recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

5.1.2 What should not be reported?

Expedited reporting is not usually required:

- for reactions which are serious but expected,
- for non-serious adverse reactions whether expected or not.

It is generally not necessary to report events that are considered unrelated to the investigational medicinal product.

5.1.3 Who should report and whom to report to?

The sponsor should report all the relevant safety information previously described to the concerned competent authorities and to the Ethics Committee concerned (see section 5.1.6.5).

The sponsor shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects (see section 5.4).

5.1.4 Managing SUSARs associated with active comparator or placebo

The sponsor must report to the competent authority and the Ethics Committee of the concerned Member States all SUSARs associated with a comparator product in the concerned clinical trial even if this product is authorised. In addition, it is recommended that the sponsor transmits them to the marketing authorisation holder and informs him of the previous notification to the competent authority. However, in all cases reporting SUSARs from a clinical trial to the competent authority should only take place through the sponsor.

Events associated with placebo will usually not satisfy the criteria for a serious adverse drug reaction and therefore for expedited reporting. However, where SUSARs are associated with placebo (e.g. reaction due to an excipient), it is recommended that the sponsor report such cases.

5.1.5 When to report?

5.1.5.1 Fatal or life-threatening SUSARs

The competent authority and the Ethics Committee in the concerned Member States should be notified as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the competent authority and the Ethics Committee in the concerned Member States within an additional eight calendar days.

5.1.5.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues, described in section 5.1.1.2, must be reported to the competent authority and the Ethics Committee in the concerned Member States as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

5.1.6 How to report?

5.1.6.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria defining a valid case report are met:

- a) a suspected investigational medicinal product,
- b) an identifiable subject (e.g. study subject code number),
- c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
- d) an identifiable reporting source,
- e) the mandatory administrative information as defined in ICH E2B(M)⁵ in the note for guidance on clinical safety data management. e.g. the unique case identifier (i.e. sponsor's case identification number) where applicable,
- f) a study protocol number e.g. EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number where applicable.

5.1.6.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. The sponsor should report further relevant information after receipt as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

5.1.6.3 Format of the SUSARs reports

Save in exceptional circumstances electronic reporting should be the expected method for expedited reporting of SUSARs to the competent authority(ies) and EudraVigilance. The format and content are defined by the relevant Community Guidance documents. Paper reporting should be exceptional and in line with the 'Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in pharmacovigilance during the pre- and post- authorisation phase in the European Economic Area (EEA)', Doc. Ref. EMEA/115735/2004 (adopted at Community level in September 2004)⁶.

The data elements to be included in the case reports are given in the ICH E2B(M). However, no matter what the form or format used, it is important that the basic information/data elements described in Annex 3, when available, be included in any expedited report (some items may not be relevant, depending on the circumstances; for initial expedited reporting see also section 5.1.6.1).

⁵ ICH E2B(M) guideline 'Maintenance of the ICH guideline on clinical safety data management: data elements for transmission of Individual Case Safety Reports E2B(M). Recommended for Adoption at Step 4 of the ICH Process on 17 July 1997 and amended for Maintenance on 10 November 2000 by the ICH Steering Committee (Including the Post Step 4 corrections agreed by the Steering Committee on 5 February 2001) CPMP/ICH/287/95 modification corr.'

⁶ <http://www.emea.eu.int/pdfs/human/phvwp/115735en.pdf>

The current version of MedDRA or the previous one to it should be used for the coding of adverse reactions terms⁷. Lower level terms should be used.

5.1.6.4 Form and format of the reports about other important safety issues also qualifying for expedited reporting

Other important safety issues also qualifying for expedited reporting (see section 5.1.1.2) should be notified by a letter under the heading of safety report. The first page of the report should reference the EudraCT number, the title and the sponsor's trial protocol code number of the trial to which it refers and points of concern summarised in a short section.

5.1.6.5 How to inform the Ethics Committee?

In accordance with national legislation Member States may provide that the concerned Ethics Committee only receive expedited individual reports of SUSARs that occurred in subjects who have been recruited in the concerned trial in that Member State. In this case, it is strongly recommended that:

- a) All SUSARs from other Member States and, where applicable, from third countries, are periodically reported at least every 6 months as a line listing accompanied by a brief report by the sponsor highlighting the main points of concern. Those periodic reports should only include SUSARs reported within the period covered by the report. A copy of the report should be sent to the concerned competent authority.
- b) Any changes increasing the risk to subjects and any new issues that may affect adversely the safety of the subjects or the conduct of the trial should also be provided as soon as possible, but no later than fifteen days.

5.1.7 SUSARs identification and management of follow-up and duplicate reports

Each initial and follow-up SUSAR report should contain enough information to allow identification of duplicate reports. Particularly, the identification code of the patient who experienced a SUSAR should be unique in the same clinical trial whatever the number of SUSARs and the time at which they occurred.

If duplicates are identified by the sponsor, the concerned competent authority(ies), the European Medicines Agency (EMA), and the concerned Ethics Committee shall be informed accordingly.

In accordance with national legislation, sponsors may be able to fulfil their obligation to reports SUSARs to the Member State competent authority by reporting them directly to the EMA database established under Article 17(3)(a) of Directive 2001/20/EC. This will avoid duplicate reporting to the EMA database where the same trial is conducted at sites in more than one Member State.

5.1.8 Managing adverse reactions/events in blinded trials

As a general rule treatment codes should be broken by the sponsor before reporting a SUSAR to the competent authority and the Ethics Committee of the concerned Member States.

Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse event may be a serious adverse reaction unexpected or otherwise judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also

⁷ See <http://www.eudravigilance.org/human/meddra01.asp> for details.

recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for data-analysis and interpretation of results at the study's conclusion. The unblinding of single cases by investigators in the course of a clinical trial should only be performed if relevant for the safety of the trial subject.

It is recommended that in case of a blinded study, the case is assessed for seriousness, expectedness and causal relationship assuming that the tested investigational medicinal product caused the reaction. If the case appears to be a SUSAR, then the blinding should be broken. Then three possibilities resulting from the procedure of unblinding must be considered:

- a) If the product administered to the subject is the tested investigational medicinal products, the case would be reported as a SUSAR to the relevant competent authorities and the relevant Ethics Committees.
- b) If the product administered to the subject is a comparator with a marketing authorisation, the adverse reaction should be reassessed for expectedness according to the summary of product characteristics as identified in the study protocol. If the adverse reaction is unexpected then the SUSAR should be reported; otherwise it is an expected serious adverse reaction and not reportable on an expedited basis.
- c) Events associated with placebo will usually not satisfy the criteria for a serious adverse drug reaction and therefore for expedited reporting. However, where after unblinding SUSARs are associated with placebo, it is the sponsor's responsibility to report such cases.

5.1.9 Managing adverse reactions/events in trials with high morbidity and high mortality diseases and where efficacy end-points could also be SUSARs

For trials in high morbidity and/or high mortality disease, where efficacy end-points could also be adverse reactions reported as SUSARs or when mortality or another "serious" outcome (that may potentially be reported as a SUSAR) is the efficacy endpoint in a clinical trial, the integrity of the clinical trial may be compromised when the blind is systematically broken. Under these and similar circumstances, it may be appropriate to reach agreement with competent authorities in advance concerning serious events that would be treated as disease-related and not subject to systematic unblinding and expedited reporting. Modalities for reporting these adverse reactions must be clearly defined in the protocol.

For such trials, sponsors are strongly encouraged to appoint an independent Data Monitoring Committee in order to review safety data on the ongoing trial on a regular basis and when necessary to recommend to the sponsor whether to continue, modify or terminate the trial. The composition and operation of a Data Monitoring Committee must be described in the protocol. The Data Monitoring Committee opinion and recommendations should be notified as soon as possible by the sponsor to the competent authority and the Ethics Committee in the concerned Member State where they qualify for expedited reporting (see section 5.3.1). However cases of SUSARs, in these same studies, that are not efficacy endpoints should be reported as usual. The Guideline on data monitoring committee by EMEA should be followed⁸.

⁸ The guideline is under public consultation

5.2 Annual safety reports

In addition to the expedited reporting, sponsors shall submit, once a year throughout the clinical trial or on request a safety report to the competent authority and the Ethics Committee of the concerned Member States, taking into account all new available safety information received during the reporting period. The aim of the annual safety report is to describe concisely all new safety information relevant for one or several clinical trial(s) and to assess the safety conditions of subjects included in the concerned trial(s).

The annual safety report should be the same for the competent authorities concerned and the Ethics Committee concerned.

5.2.1 Content of the annual safety report of a clinical trial

The annual safety report of a clinical trial should have three parts:

- Part 1: Analysis of the subjects' safety in the concerned clinical trial.
- Part 2: A line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the concerned trial, including also serious adverse reactions from third countries.
- Part 3: An aggregate summary tabulation of suspected serious adverse reactions that occurred in the concerned trial.

Part 1: Analysis of the subjects' safety of the concerned clinical trial

This section provides a concise description and safety analysis of all relevant findings that could have a significant impact on the clinical trial population and a benefit-risk evaluation for the clinical trial concerned.

It should describe in a concise way, all new and relevant findings, known by the sponsor, related to the safety of the subjects in the concerned trial, including all new findings related to the safety of investigational medicinal product treatments or other treatments used in the trial and any other findings related to clinical trial procedures. The concept of new findings for an investigational medicinal product refers to information not already present in the reference document in force at the beginning of the period covered by the report (investigator's brochure or summary of product characteristics). Conclusions and/or recommendations from the Data Monitoring Committee, if any, should be discussed and attached to the report.

It should also analyse the safety profile of the tested investigational medicinal product and its implication for subjects' exposure, taking into account all available safety data including drop outs for safety reasons. When relevant, the following points should be considered:

- a) relation with dose, duration, time course of the treatment;
- b) reversibility;
- c) evidence of previously unidentified toxicity in the trial subjects;
- d) increased frequency of toxicity;
- e) overdose and its treatment;
- f) interactions or other associated risks factors;
- g) any specific safety issues related to special populations, such as the elderly, children or any other at risk groups;
- h) positive and negative experiences during pregnancy or lactation;
- i) abuse;
- j) risks which might be associated with the investigation or diagnostic procedures of the clinical trial;
- k) risks which might be associated with insufficient quality of the investigational medicinal product.

The report should also consider supporting results of non-clinical studies or other experience with the investigational medicinal product that are likely to affect the subjects' safety.

It should be complemented with an analysis of the implications for the population of the clinical trial, such as:

- Measures previously or currently proposed to minimise the risks found, where appropriate;
- A detailed rationale for whether or not it is necessary to amend the protocol, to change or update the consent form, patient information leaflet and the investigator's brochure.

This report will not replace the request for protocol amendments, which will follow its own specific procedure.

Finally an update of the risk-benefit evaluation for the concerned clinical trial should be provided.

Part 2: Line-listings

This section should contain a trial-specific line-listing of all suspected serious adverse reactions that were reported during this trial from all sites within the period covered by the report.

The line listing provides key information but not necessarily all the details usually collected on individual cases.

It should include each subject only once regardless of how many adverse reaction terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious adverse reaction (sign, symptom or diagnosis) as judged by the sponsor.

It is possible that the same subject may experience different adverse reactions on different occasions. Such experiences should be treated as separate reports. Under such circumstances, the same subject might then be included in a line listing more than once and the line-listings should be cross-referenced when possible.

Cases should be tabulated by body system (standard organ system classification scheme).

The line listing identifiable by the sponsor's listing reference number or date and time of printing should include the information per case as described in Annex 4.

Usually there should be one listing for each trial, but separate listings might be provided for active comparator or placebo, or when appropriate and relevant for other reasons, e.g. in the same trial for different formulations, indications or routes of administration are studied. Expectedness at the time of occurrence of the suspected serious adverse reactions will be assessed with the reference document in force at the beginning of the period covered by the annual safety report.

Part 3: Aggregate summary tabulations

In addition to individual cases line listings provided in the part 2, summary tabulations of all serious adverse reactions that occurred during the trial should be provided to allow an overview of the trial. In those tabulations, serious adverse reaction terms for signs, symptoms and/or diagnoses across all patients should usually be presented. These tabulations ordinarily contain more terms than subjects. When the number of cases is very small, a narrative description would be more suitable.

The aggregate summary tabulation should specify the number of reports:

- a) for each body system
- b) for each adverse reaction term

- c) for each treatment arm, if applicable (tested investigational medicinal product, comparator or placebo, blinded treatment).

The unexpected adverse reaction terms should be clearly identified in the tabulation. As an example, the table in annex 5 can be used.

When the sponsor conducts several clinical trials in several Member States with the same tested investigational medicinal product, a single annual safety report referring to those trials is strongly recommended. In that case, it should be composed of:

- a concise global analysis on the safety profile of the tested investigational medicinal product taking into account all relevant new safety findings related to the use of the tested investigational medicinal product and an analysis of the implications of the findings for the population included in clinical trials,
- and the annual safety report relating to each clinical trial concerned.

5.2.2 Reporting time frame for annual safety report

The reporting time frame for annual reports starts with the date of the first authorisation according to the Directive 2001/20/EC of the concerned clinical trial by a competent authority in any Member State.

The anniversary of this date is designated as the cut off for data to be included in the annual safety report. The sponsor should submit annual reports within 60 days of the data lock point.

However, if a sponsor conducts several clinical trials with the same tested investigational medicinal product in any Member State, he should prepare only one safety report covering the information necessary for all those trials, the reporting period starts with the date of the authorisation for the first of these trials by the competent authority in any Member State and ends after close of the last trial in any Member State. If the sponsor is the marketing authorisation holder (MAH) of the tested investigational medicinal product, the reporting period should be aligned with the international birth date. However, the Annual Safety Report and the Periodic Safety Update Report (PSUR) must be stand-alone documents.

If a marketing authorisation is granted for the investigational medicinal product for the first time in any Member State while it is being tested in a clinical trial, the reporting time frame for the investigational medicinal product would change from the first date of authorisation of a clinical trial in a Member State to the international birth date. If a marketing authorisation was granted for the investigational medicinal product before the 1st of May 2004, the international birth date should be applied.

In case of a first-in-man trial and subsequent short term metabolism or pharmacokinetic studies the safety report should be notified within 90 days of the end of trial together with the notification of the end of the trial according to Article 10(c) of Directive 2001/20/EC. This report should contain at least an analysis of the subjects' safety and line listings, and if appropriate aggregate summary tabulations.

5.3 How to inform the investigators?

The sponsor shall inform all investigators concerned of findings that could adversely affect the safety of study subjects. If appropriate, the information can be aggregated in a line listing of SUSARs in periods as warranted by the nature of the clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the investigational medicinal product.

In the case of blinded trials the line listing should present data on all SUSARs, regardless of the medication administered (e.g. active/placebo), thereby when possible and appropriate, the

blind would be maintained and the risk of inadvertently informing the investigators with regard to the identity of the medication would be avoided.

If a significant safety issue is identified, either upon receipt of an individual case report or upon review of aggregate data, the sponsor should issue as soon as possible a communication to all investigators.

A safety issue that impacts upon the course of the clinical study or development project, including suspension of the study programme or safety-related amendments to study protocols should also be reported to the investigators.

5.4 Reporting of safety issues following completion of the clinical trial in the European Community

After termination of the clinical trial, any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the subjects who have participated in it, should be reported as soon as possible to the competent authority(ies) concerned together with proposed actions.

Annex 1: Comments on definitions and abbreviations

- **Adverse event:** *any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.*

Comment: An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product

- **Adverse reaction of an investigational medicinal product:** *all untoward and unintended responses to an investigational medicinal product related to any dose administered.*

Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

- **Unexpected adverse reaction:** *an adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).*

Comments:

- When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.
 - **Severity:** The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.
- **Serious adverse event or serious adverse reaction:** *any untoward medical occurrence or effect that at any dose*
 - *results in death,*
 - *is life-threatening*
 - *requires hospitalisation or prolongation of existing inpatients' hospitalisation,*
 - *results in persistent or significant disability or incapacity,*
 - *is a congenital anomaly or birth defect.*

Comments:

- Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

- **Concerned Member State:** *Member State in whose territory a clinical trial with the investigational product is being performed.*
- **Ethics Committee Concerned:** *Ethics Committee that gave the favourable opinion for a clinical trial on the investigational product in a Member State according to Art. 7 of the Directive 2001/20/EC.*
- **Investigators Concerned:** *Investigators, which are actively involved in running clinical trials on the tested investigational medicinal product.*
- **Data Lock-Point (cut-off date)⁹:** *The date designated as the cut off date for data to be included in a annual safety report.*
- **International Birth Date¹⁰:** *The date of the first marketing authorisation for a medicinal product granted to the marketing authorisation holder (MAH) in any country in the world.*
- **Periodic Safety Update Report (PSUR)¹¹ for a medicinal product with a marketing authorisation:** *All records of adverse reactions shall be submitted to the competent authorities in form of a periodic safety update report, either immediately upon request or periodically as follows: six monthly for the first two years after authorisation, annually for the subsequent two years, and at the time of the first renewal. Thereafter the periodic safety update report shall be submitted at five-yearly (three-yearly from November 2005) intervals together with the application for renewal of the authorisation. The periodic safety update report shall include a scientific evaluation of the benefit and risks afforded by the medicinal products.*

⁹ EudraLex Volume 9 - Pharmacovigilance: Medicinal Products for Human use and Veterinary Medicinal Products, page 146

¹⁰ EudraLex Volume 9 - Pharmacovigilance: Medicinal Products for Human use and Veterinary Medicinal Products, page 147

¹¹ Directive 2001/83/EC Article 1 No. 14 and Article 104 No. 6

Annex 2: Member States' Contact points for Reporting (will be up-dated in due course)

The Member States' contact points for reports of adverse reactions occurring in clinical trials on human medicinal products are as follows:

Member State	Contact Point
Belgium	Federal Public Service Health, Food Chain Safety and Environment Directorate-General Medicinal Products Unit IX – Clinical trials Bischhoffsheim 33, 1 st floor 1000 Brussels Belgium Phone: + 32 (0) 2 227 55 77 Fax: + 32 (0) 2 227 55 31
Denmark	The Danish Medicines Agency Clinical Trials, Inspection and Enforcement Division Axel Heides Gade 1 DK-2300 Copenhagen S Phone: + 45 44 88 95 95 Fax: + 45 44 88 93 14 Internet: www.dkma.dk
Finland	Clinical trials Enforcement & Inspection National Agency for Medicines PO Box 55 FIN-00301 Helsinki Finland Phone: +358 9 473341 Fax: +358 9 47334 323 Internet: www.nam.fi
France	Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) DEMEB/Unité Essais Cliniques 143/147, Boulevard Anatole France 93285 Saint-Denis Cedex Phone: +33 1 55 8736 43 Fax: +33 1 55 8736 42 Internet : www.afssaps.sante.fr
Germany	Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) (Federal Institute for Drugs and Medical Devices) Kurt-Georg-Kiesinger-Allee 3 D-53175 Bonn Phone: +49 228 207 30 Fax: +49 228 207 5207 Internet: www.bfarm.de Paul-Ehrlich-Institut (PEI) Paul-Ehrlich-Str. 51-59 D-63225 Langen Phone: +49 6103 77 1010/1011 Fax: +49 6103 77 1263 Internet: www.pei.de

Member State	Contact Point
Greece	National Organization for Medicines (EOF) Division of Pharmaceutical Studies and Research 284 Mesogeion Avenue 15562 Athens Greece Phone: +30 210 6507200 Fax: +30 210 6549585 Internet: www.eof.gr
Italy	Italian Medicines Agency – AIFA Via della Sierra Nevada, 60 00 144 Roma Phone: +39 06 5994 4311 Fax: +39 06 5994 4110
Ireland	Drug Safety Associate, Pharmacovigilance Unit, Irish Medicines Board; Earlsfort Centre Earlsfort Terrace Dublin 2 Ireland Phone: +353 1 676 4971 Fax: +353 1 676 2517 Internet: www.imb.ie
Luxembourg	Direction de la Santé Division de la Pharmacie et des Médicaments Villa Lowigny Allée Marconi L-2120 Luxembourg Phone: +352 478 55 93/55 90 Fax: +352 26 20 01 40/47
Netherlands	- College ter Beoordeling van Geneesmiddelen/Medicines Evaluation Board PO Box 16229 2500 BE Den Haag The Netherlands Phone: +31 70 356 7400 Fax: +31 70 356 7515 E-mail: info@cbg-meb.nl - CCMO Central Committee on Research Involving Human Subjects (CCMO) PO Box 16302 7500 BH The Hague The Netherlands Phone: + 31 70 3406700 Fax: + 31 70 3406737 E-mail: ccmo@ccmo.nl Internet: www.ccmo.nl

Member State	Contact Point
Portugal	<p>INFARMED, Departamento de Farnacovigilancia, Sector de Reaccoes Adversas a Medicamentos Parque da Saude de Lisboa Av. Do Brasil, 53 1749-004 Lisboa Portugal Phone: +351 21 7987 100/7142 Fax: +351 21 7987 100 Internet: www.infarmed.pt</p>
Spain	<p>- Agencia Espanola de Medicamentos y Productos Sanitarios Division de Farmacologia y Evaluacion Clinica C/ Alcalá, 56 28071 Madrid Spain Fax: +34 91 822 5161</p> <p>- When the investigational medicinal product is marketed in Spain and used under the terms of market authorisation: Agencia Espanola de Medicamentos y Productos Sanitarios Division de Farmacoepidemiologia y Farmacovigilancia C/ Alcalá, 56 28071 Madrid Spain Fax: +34 91 596 78 91</p>
Sweden	<p>Pharmacovigilance Unit Medicinal Products Agency P.O. Box 26 S-751 03 Uppsala Sweden Phone: +46 18 17 46 00 Fax: +46 18 54 85 66 E-mail: registrator@mpa.se Internet: www.mpa.se</p>
United Kingdom	<p>MHRA Clinical Trials Unit Market Towers, 12th Floor 1 Nine Elms Lane London SW8 5 NQ Phone: +44 (0) 207 084 2327 Fax: +44 (0) 207 084 2443 E-mail: salma.syed@mhra.gsi.gov.uk</p>

New Member States

Member State	Contact Point
Cyprus	The Registrar Drugs Council Pharmaceutical Services, Ministry of Health 1475 Lefkosia Cyprus Phone: +357 22 407 132 Fax: +357 22 407 149
Czech Republic	State Institute for Drug Control – Branch of Clinical Trials and Pharmacovigilance Šrobárova 48 100 41 Praha 10 Czech Republic Phone: +420 272 185 817 Fax: +420 272 185 816 E-mail: klin.sekret@sukl.cz
Estonia	Katrin Kiisk State Agency of Medicines 19 Ravila Street 50411 Tartu Estonia Fax: +372 737 4142 E-mail: katrin.kiisk@sam.ee
Hungary	National Institute of Pharmacy Pharmacovigilance Department Budapest Zrínyi u.3. Hungary H-1051 P.O.B.450
Latvia	Janis Ozolins, Head of the Board of State Agency of Medicines, 15 Jersikas street, Riga, LV 1003 Phone: +371 70784 00 Fax: +371 70784 28 E-mail: info@vza.gov.lv
Lithuania	Preclinical and Clinical Trials Division State Medicines Control Agency of Lithuania Traku str. 14, LT-01132 Vilnius Lithuania Phone: +370 5 2639547 Fax: +370 5 2614552 E-mail: nr.iktk@vvkt.lt Internet: www.vvkt.lt

Member State	Contact Point
Malta	Pharmacovigilance Section Post-Licensing Directorate Medicines Authority 198, Rue D'Argens Gzira, GZR 03 Malta Phone: +356 23439153 Fax: +356 23439158 E-mail: postlicensing.mru@gov.mt Internet: www.health.gov.mt/mru
Poland	Office for Medicinal Products, Medical Devices and Biocides, Central Register of Clinical Trials Zabkowska 41 03-736 Warsaw Phone : +48 22 492 1292 Fax: +48 22 492 1299 E-mail: marcin.graf@urpl.gov.pl Internet: www.urpl.gov.pl
Slovak Republic	State Institute for Drug Control Kvetná 11 Section of drug safety and clinical trials 825 08 Bratislava 26 Slovak Republic Phone: +421 2 5293 17 34 Fax: +421 2 5293 17 34 E-mail: trial-sukl@sukl.sk Internet: www.sukl.sk
Slovenia	Agency for Medicinal Products and Medical Devices Mali trg 6, 1000 Ljubljana, Slovenia Phone: +386 1 47 86 240 Fax: +386 1 47 86 260 E-mail: arszmp.mz@gov.si
EFTA	
Norway	Norwegian Medicines Agency Section for clinical trials Sven Oftedalsvei 6 NO-0950 OSLO Norway Phone: +47 22 89 77 00 Fax: +47 22 89 77 99 Internet: www.noma.no E-mail: klut@noma.no

Annex 3 Data Elements for Suspected Unexpected Serious Adverse Reaction (SUSAR) report

1. Clinical trial identification¹:

- Clinical trial identification (EudraCT number, if applicable or the sponsor's trial protocol number),

2. Subject's details:

- Sponsor's subject identification number¹²,
- Initials, if applicable,
- Gender,
- Age and/or date of birth,
- Weight,
- Height,

3. Suspected investigational medicinal product(s):

- Name of the investigational medicinal product or brand name as reported,
- International non-proprietary name (INN),
- Batch number,
- Indication(s) for which suspect investigational medicinal product was prescribed or tested,
- Dosage form and strength,
- Daily dose and regimen (specify units e.g. mg, ml, mg/kg),
- Route of administration,
- Starting date and time of day,
- Stopping date and time, or duration of treatment
- Unblinding: yes/no/not applicable; results¹:
- * Investigator's causality assessment
- * Sponsor's causality assessment
- * Comments, if relevant (e.g. causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s).

4. Other treatment(s):

- For concomitant medicinal products (including non prescription/OTC medicinal products) and non-medicinal product therapies provide the same information as listed above for the suspected investigational medicinal product.

5. Details of suspected Adverse Drug Reaction(s):

- Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible attempts should be made to establish a specific diagnosis for the reaction,
- Reaction(s) in MedDRA terminology¹ (lowest level term)¹³
- Start date (and time) of onset of the reaction,
- Stop date (and time) or duration of the reaction,
- De-challenge and re-challenge information,

¹² Data not listed in CPMP/ICH/377/95

¹³ EMEA recommendations and ICH E2B (M).B2i 1

- Setting (e.g. hospital, out-patient clinic, home, nursing home),
- Outcome: information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available,
- Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse, family history, findings from special investigations.

6. Details on reporter of event/suspected adverse reactions:

- Name,
- Address,
- Telephone number,
- Profession (speciality).

7. Administrative and Sponsor details:

- Date of this report,
- Source of report: from a clinical trial (provide details if not in Eudract¹, from the literature (provide copy), spontaneous, other,
- Date event report was first received by sponsor,
- Country in which reaction occurred,
- Type of report filed to authorities: initial or follow-up (first, second, etc),
- Name and address of sponsor/manufacturer/company,
- Name, address, telephone number and fax number of contact person in reporting sponsor,
- identifying regulatory code or number for marketing authorisation dossier or clinical investigation process for the suspected product (for example IND number, NDA number),
- Case reference number (sponsor's/manufacturer's identification number for the case) (this number must be the same for the initial and follow-up reports on the same case).

Annex 4 Content of line listing

The line listing identifiable by the sponsor listing reference number or date and time of printing should include the following information per case:

- a) clinical trial identification,
- b) study subjects identification number in the trial,
- c) case reference number (Case-ID-Number) in the sponsor's safety database for medicinal products,
- d) country in which case occurred,
- e) age and sex of trial subject,
- f) daily dose of investigational medicinal product, (and, when relevant, dosage form and route of administration),
- g) date of onset of the adverse reaction;
if not available, best estimate of time to onset from therapy initiation. For an adverse reaction known to occur after cessation of therapy, estimate of time lag if possible,
- h) dates of treatment. (if not available, best estimate of treatment duration),
- i) adverse reaction: description of reaction as reported, and when necessary as interpreted by the sponsor; where medically appropriate, signs and symptoms can be lumped into diagnoses. MedDRA should be used,
- j) patient's outcome (e.g. resolved, fatal, improved, sequelae, unknown). This field should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions,
- k) comments, if relevant
(e.g. causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge / rechallenge results if available),
- l) unblinding results in the case of unblinded SUSARs expectedness at the time of the occurrence of the suspected serious adverse reactions, assessed with the reference document (i.e. investigator's brochure) in force at the beginning of the period covered by the report.

Annex 5 Example for an Aggregate Summary Tabulation

Number of reports by terms (signs, symptoms and diagnoses) for the trial n°:
 (An * indicates an example of a SUSAR)

<i>Body system / ADR term</i>	<i>Verum</i>	<i>Placebo</i>	<i>Blinded</i>
<i>CNS</i>			
<i>Hallucinations*</i>	<i>2</i>	<i>2</i>	<i>0</i>
<i>Confusion*</i>	<i>1</i>	<i>1</i>	<i>0</i>
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<i>Sub-total</i>	<i>3</i>	<i>3</i>	<i>0</i>
<i>CV</i>			
...			

<i>Sub-total</i>			