

## **DECISION**

**No. 26/28.09.2007**

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

The Scientific Council of the National Medicines Agency, set up based on Minister of Public Health Order No. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 29.02.2008, in accord with Article 10 of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as further amended, agrees on the following

## **DECISION**

**Art. 1.** – The Guideline on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use is approved, according to the Annex which is integral part of this Decision.

**Art. 2.** – On the date of the coming into force of this Decision, the Scientific Council Decision No. 22/01.10.2004 on approval of the Guideline on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, approved through Minister of Public Health Order No. 1628/13.12.2004, is repealed.

**PRESIDENT  
of the Scientific Council  
of the National Medicines Agency**

**Acad. Prof. Dr. Victor Voicu**

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

**CHAPTER I**  
**Introduction**

Art. 1. – This Guideline is a translation and an adaptation into Romanian of Guideline ENTR/CT 3 (2006) on the collection, verification and presentation of adverse reaction reports arising from clinical trial son medicinal products for human use.

**CHAPTER II**  
**Legal basis**

Art. 2. - Art. 65 of the Minister of Public Health Order No. 904/2006 on approval of the Regulations on the implementation of GCP rules carried out on medicinal products for human use, implies the publication by the National Medicines Agency (NMA) of several guidelines on the collection, verification and presentation of adverse event/reaction reports along with decodification procedures in case of serious and unexpected adverse reactions; this Guideline is an answer to the obligations stipulated in the article concerned.

Art. 3. – According to Art. 58 and 59 of the Minister of Public Health Order No. 904/2006, the investigator shall report all serious events (SEs) immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting.

Art. 4. - 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.

Art. 5. – According to Article 60 of the Minister of Public Health Order No. 904/2006, the investigator shall supply the sponsor and the Ethics Committee with any additional requested information, notably for reported death of a subject.

Art. 6. – According to Art. 61 of the Minister of Public Health Order No. 904/2006 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.

Art. 7. – According to Art. 62 (1) and (2) of the Minister of Public Health Order No. 904/15.12.2006 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.

Art. 8. – According to Art. 62 (4) of the Minister of Public Health Order No. 904/2006 the sponsor should also inform the investigators.

Art. 9. – According to Art. 63 of the Minister of Public Health Order No. 904/2006 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 (SARs) which have occurred over this period.

### **Scope**

Art. 10. - 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.

## **CHAPTER III**

### **General principles**

Art. 11. – (1) This guidance applies to all clinical trials on medicinal products for human use within the scope of the Minister of Public Health Order No. 904/2006 conducted within the European Community (with at least one investigator site in the Community).

(2) 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.

## **CHAPTER IV**

### **Definitions**

Art. 12. – The definitions of the Minister of Public Health Order No. 904/2006, Article 21, are applicable in this Guideline.

## CHAPTER V

### **Investigator's responsibilities**

Art. 13. - The investigator's responsibilities with regard to notification of adverse events are set out in the Minister of Public Health Order No. 904/2006.

## CHAPTER VI

### **Sponsor's responsibilities**

#### VI.1 Miscellanea

Art. 14. - The sponsor is responsible for the ongoing safety evaluation of the investigational medicinal product(s) during the study.

Art. 15. - The sponsor is responsible for the prompt notification to all concerned investigators, the Ethics Committee and competent authorities 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 the national legislation in force.

Art. 16. - 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.

#### VI.2. Recording and evaluation of Adverse Events (AEs)

Art. 17. - 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.

Art. 18. - Individual adverse events should be evaluated by the investigator and where indicated by the Guideline in chapter VI.3, 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.

Art. 19. - 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.

Art. 20. - 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).

#### VI.2.1. Assessment of seriousness

Art. 21. - Seriousness shall be determined according to the definition in Article 21 of the Minister of Public Health Order No. 904/2006 taking into account the comments presented in Annex 1.

#### VI.2.2. Assessment of causality

Art. 22. - Causality shall be determined according to the definition of an adverse reaction as given in Article 21(n) of the Minister of Public Health Order No. 904/2006 taking into account the comments presented in Annex 1.

Art. 23. - (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.

(2) The causality assessment given by the investigator should not be downgraded by the sponsor.

(3) 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.

#### VI.2.3. Sponsor's assessment of expectedness

Art. 24. - (1) The definition of the term "unexpected adverse reaction" is given in Article 21 of the Minister of Public Health Order No. 904/2006.

(2) 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 exposed in the IMP file.

(3) The expectedness of an adverse reaction shall be determined by the sponsor according to the reference documents.

(4) 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 (SPC) for an authorised medicinal product in the European Community, which is being used according to the terms and conditions of the marketing authorisation).

(5) When the investigational medicinal products has a marketing authorisation in several Member States with different SPCs, the sponsor should select the most appropriate SPC, with reference to patient safety, as a reference document for assessing expectedness.

(6) The reference document is the same for the whole clinical trial in all the Member States concerned; this should be clearly identified in the

protocol and attached to the Clinical Trial Application, in an acceptable language (Romanian/English) and mentioned in the covering letter.

#### VI.2.4. Data protection of trial subjects

Art. 25. - The Community standards of confidentiality must always be maintained in accordance with the national legislation on data protection.

#### VI.3. Reporting of serious adverse reactions (SARs)

##### VI.3.1. Standards for expedited reporting

##### VI.3.1.1. Information requiring expedited reporting

##### VI.3.1.1.1. Suspected Unexpected Serious Adverse Reactions (SUSARs)

Art. 26. - 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)”.

Art. 27. - 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:

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 occurring outside the concerned clinical trial;

- 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) the report should be in accordance with the Regulation (EC) No. 726/2004, Directive 2001/83/EC and

(ii) if it occurs in a clinical trial, the report should comply with the ‘Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions – SUSARs - (Eudravigilance – Clinical Trial Module)’.

- Where the investigational medicinal product has a marketing authorisation in any Member State, and the sponsor is not the marketing authorisation holder (MAH), 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.

- Where the investigational medicinal product does not have a marketing authorisation (MA) in any Member State of the European 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.

#### VI.3.1.1.2. Other safety issues requiring expedited reporting

Art. 28. - 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 product 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.

#### VI.3.1.2. Information that should not be reported

Art. 29. –Expedited reporting is not usually required in the following situations:

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

Art. 30. - It is generally not necessary to report events that are considered unrelated to the investigational medicinal product.

#### VI.3.1.3. Who should report and whom to report to?

Art. 31. - The sponsor should report all the relevant safety information previously described to the concerned competent authorities and to the Ethics Committee concerned (see section VI.3.1.6.5).

Art. 32. - The sponsor shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects (see section VI.4).

#### VI.3.1.4. Managing SUSARs associated with active comparator or placebo

Art. 33. - 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 medicinal 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 (NMA) should only take place through the sponsor.

Art. 34. - 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.

#### VI.3.1.5. When to report?

##### VI.3.1.5.1. Fatal or life-threatening SUSARs

Art. 35. - The competent authorities 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.

Art. 36. - In each case relevant follow-up information should be sought and a report completed as soon as possible; this report should be communicated to the competent authorities and the Ethics Committee in the concerned Member States within an additional eight calendar days.

#### VI.3.1.5.2. Non fatal and non life-threatening SUSARs

Art. 37. - All other SUSARs and safety issues, described in section VI.3.1.1.2, must be reported to the competent authority and the Ethics Committees 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.

#### VI.3.1.6. How to report

##### VI.3.1.6.1. Minimum criteria for initial expedited reporting of SUSARs

Art. 38. - (1) Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting.

(2) 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 with the investigational medicinal product,
- d) an identifiable reporting source,
- e) the mandatory administrative information as defined in ICH E2B(M), 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.

##### VI.3.1.6.2. Follow-up reports of SUSARs

Art. 39. - 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 of follow-up reports.

Art. 40. - In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular adverse reaction.

#### VI.3.1.6.3. Format of the SUSARs reports

Art. 41. - Electronic reporting should be the expected method for expedited reporting of SUSARs to the competent authority(ies) and EudraVigilance.

Art. 42. - 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).

Art. 43. - 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 2, 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 VI.3.1.6.1).

Art. 44. - The current version of MedDRA or the previous one to it should be used for the coding of adverse reactions terms; lower level terms should be used.

#### VI.3.1.6.4. Form and format of the reports about other important safety issues also qualifying for expedited reporting

Art. 45. - Other important safety issues also qualifying for expedited reporting (see section VI.3.1.1.2) 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.

#### VI.3.1.6.5. How to inform the Ethics Committee?

Art. 46. - The concerned Ethics Committee should only receive expedited individual reports of SUSARs that occurred in subjects who have been recruited in Romania.

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.

#### VI.3.1.7. SUSARs identification and management of follow-up and duplicate reports

Art. 47. - Each initial or 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.

Art. 48. - 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.

Art. 49. - In accordance with national legislation, sponsors may be able to fulfil their obligation to report 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.

#### VI.3.1.8. Managing adverse reactions/events in blinded trials

Art. 50. - 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.

Art. 51. - 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 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.

Art. 52. - 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.

Art. 53. - 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 medicinal product administered to the subject is the tested investigational medicinal product, the case would be reported as a SUSAR to the relevant competent authorities and the relevant Ethics Committees.

b) If the medicinal product administered to the subject is a comparator with a marketing authorization (MA), 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.

VI.3.1.9. Managing adverse reactions/events in trials with high morbidity and high mortality diseases, where efficacy end-points could also be SUSARs

Art. 54. - 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.

Art. 55. - Modalities for reporting these adverse reactions must be clearly defined in the protocol.

Art. 56. - (1) 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.

(2) 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 VI.3.1).

(3) 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 followed.

#### VI.3.2. Annual safety reports

Art. 57. – (1) 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.

(2) 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).

Art. 58. - In case the sponsor carries out several clinical trials on the same investigational medicinal products, the annual safety report should contain a concise overall analysis of the present safety profile based on the experience from all clinical trials carried out by the sponsor and from all data available; this overall analysis should be the same for the competent authorities concerned and the Ethics Committee concerned.

##### VI.3.2.1. Content of the annual safety report of a clinical trial

Art. 59. - The annual safety report of a clinical trial should have three parts:

- a) Analysis of the subjects' safety in the concerned clinical trial;
- b) 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;
- c) An aggregate summary tabulation of suspected serious adverse reactions that occurred in the concerned trial.

##### VI.3.2.1.1. Report on the safety of the subjects involved in a clinical trial

Art. 60. – (1) The sponsor should provide a concise decision and safety and risk/benefit analysis for the concerned clinical trial, briefly describing all new relevant findings known, related to the safety of the treatment with investigational medicinal products or of other treatments used in the trial and provide a critical analysis taking into account their influence

on the trial subjects; any other findings related to clinical trial procedures should also be described.

(2) The concept of new findings for an investigational medicinal product refers to information not already present in the reference documents in force at the beginning of the period covered by the report (investigator's brochure or summary of product characteristics).

Art. 61. - Conclusions and/or recommendations from the Data Monitoring Committee, if any, should be discussed and attached to the report.

Art. 62. – 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 procedures or diagnosis during the clinical trial;
- k) risks which might be associated with insufficient quality of the investigational medicinal product.

Art. 63. – (1) 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.

(2) The report should be complemented with an analysis of the implications for the population of the clinical trial, such as:

- a) Measures previously or currently proposed to minimise the risks found, where appropriate;
- b) 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.

(3) Finally an updated risk-benefit evaluation for the concerned clinical trial should be provided.

#### VI.3.2.1.2. Line-listings

Art. 64. - This annual report 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.

Art. 65. - (1) The line listing provides key information but not necessarily all the details usually collected on individual cases.

(2) 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.

Art. 66. - 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.

Art. 67. - Cases should be tabulated by body system (standard organ system classification scheme).

Art. 68. - 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 3 of this Guideline.

Art. 69. - 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).

Art. 70. - Expectedness at the time of occurrence of the suspected serious adverse reactions will be assessed with the reference documents in force at the beginning of the period covered by the annual safety report.

#### VI.3.2.1.3. Aggregate summary tabulations

Art. 71. - (1) In addition to line listings, in order to form an overview of the trial, tabulations should be edited, containing all terms relating to serious adverse reactions, symptoms and/or diagnoses for all patients.

(2) In those tabulations, the number of terms is usually higher than the number of subjects.

Art. 72. - When the number of cases is very small, a narrative description would be more suitable.

Art. 73. 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).

Art. 74. - The unexpected adverse reaction terms should be clearly identified in the tabulation; as an example, the table in Annex 4 can be used in this Guideline.

Art. 75. - When the sponsor conducts several clinical trials in several EU 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) 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 as well as an analysis of the implications of the findings for the population included in clinical trials,
- b) the annual safety report relating to each clinical trial concerned.

#### VI.3.2.2. Reporting time frame for annual safety report

Art. 76. – (1) The reporting time frame for annual reports starts with the date of the first authorisation of the concerned clinical trial by a competent authority in any Member State.

(2) 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.

Art. 77 – 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.

Art. 78. - 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.

Art. 79. – 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 1<sup>st</sup> of May 2004, the international birth date should be applied.

Art. 80. - 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 the Minister of Public Health Order No. 904/2006 Art. 45 (c); this report should contain at least an analysis of the subjects' safety and line listings, and if appropriate aggregate summary tabulations.

#### VI.4. How to inform the investigator?

Art. 81. - (1) The sponsor shall inform all investigators concerned of findings that could adversely affect the safety of study subjects.

(2) 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.

Art. 82. - 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.

Art. 83. - (1) 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.

(2) 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.

#### VI.5. 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 risk/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.

## **Comments on definitions and abbreviations**

**Adverse event (AEs):** 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 concerned 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 the presence of a causal relationship.

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

**Ethics Committee Concerned:** Ethics Committee that gave the favourable opinion for a clinical trial on the investigational product in an involved Member State according to Art. 32 of the Minister of Public Health Order No. 904/2006.

**Investigators Concerned:** Investigators, which are actively involved in running clinical trials on the tested investigational medicinal product.

**Data Lock-Point (cut-off date):** The date designated as the cut off date for data to be included in an annual safety report.

**International Birth Date:** The date of the first marketing authorisation for a medicinal product granted in any country in the world.

**Periodic Safety Update Report (PSUR) 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 PSUR shall include a scientific evaluation of the benefit and risks afforded by the medicinal product.

**Data elements for Suspected Unexpected Serious Adverse  
Reaction (SUSAR) report**

1. Clinical trial identification:

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

2. Subject's details:

- Sponsor's subject identification number,
- 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; results:

\*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 medicinal product(s).

4. Other treatments:

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 terminology<sup>1</sup> (lowest level term)
- Start date (and time) of onset of the adverse reaction,
- Stop date (and time) or duration of the reaction,
- De-challenge and re-challenge information,
- 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 Eudract, from the literature (provide copy), spontaneous, other,
- Date event report was first received by sponsor,
- country in which the adverse reaction occurred
- Type of report filed to authorities: initial or follow-up (first, second, etc),
- Name and address of sponsor/manufacture r/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
- Case reference number (sponsor's/manufacture r's identification number for the case) (this number must be the same for the initial and follow-up reports on the same case).

### **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 in the sponsor's safety database for investigational medicinal products;
- d) country in which the 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 is the one 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;
- 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 adverse reactions;
- k) comments, if relevant (e.g. causality assessment if the sponsor disagrees with the reporter; concomitant medication suspected to play a role in the reactions directly or by interaction; indication treated with suspect medicinal product(s);
- 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.

**Example for an Aggregate Summary Tabulation**

Number of reports by terms (signs, symptoms and diagnoses) for trial no.:

Body system/ ADR term	Verum	Placebo	Blinded
CNS			
Halucinations*	2	2	0
Confusion*	1	1	0
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Sub-total	3	3	- 0
CV			
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Sub-total			

An \* indicates an example of a SUSAR