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EUDRAVIGILANCE EXPERT WORKING GROUP RESPONSE TO THE EUROPEAN COMMISSION PUBLIC CONSULTATION DOCUMENT –

"Draft detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use ('CT-3')"

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1 Executive Summary

The EudraVigilance Expert Working Group (EV-EWG) welcomes the Public Consultation Document (Ref. sanco.ddgl.c.8(2010)384118) published on 17 June 2010 regarding the revision of the existing Detailed Guidance (ENTR/CT 3[a] and ENTR/CT 4[b]) of the European Commission (EC) on adverse reactions reporting in clinical trials.

The proposed draft Detailed Guidance addresses many of the issues which were highlighted by the EV-EWG in its response to the Public Consultation Paper on the Assessment of the Functioning of the Clinical Trials Directive 2001/20/EC (Doc. Ref. EMA/764025/2009).

The draft Detailed Guidance aims to facilitate the harmonisation and simplification of Suspected Unexpected Serious Adverse Reactions (SUSARs) reporting in the European Economic Area (EEA) and the implementation of a fully functioning EudraVigilance Clinical Trial Module (EVCTM) which supports the protection of the health and safety of clinical trial subjects.

In response to the current public consultation, the EV-EWG has prepared this document, which focuses mainly on points related to the electronic reporting of cases of SUSARs, taking into account some of the aspects already addressed through published Questions and Answers documents which were initially elaborated by the EV-EWG.

The EV-EWG comments are presented as follows:

- General comments
- Specific aspects for each of the chapters of the draft Detailed Guidance.

2 General comments

i. The role and responsibilities of all the involved parties in the monitoring of the safety of a clinical trial should be clearly defined taking into account the relevant articles of the Directive 2001/20/EC. This was previously addressed in Chapter 4 of the Detailed Guidance ENTR/CT 3 and in Chapter 6 of the Detailed Guidance ENTR/CT 4 and it could be summarised after Chapter 1.3 of the draft Detailed Guidance. This refers in particular to the responsibilities of

   - The investigators in reporting serious adverse events and reactions as well as providing additional information,
   - The sponsors as regards the ongoing safety evaluation of the Investigational Medicinal Product (IMP) and the prompt notification of the National Competent Authorities (NCAs), Ethics Committees and investigators about any findings which impact on the safety of the clinical trial subjects,
   - The NCAs in assessing the safety and the benefit risk balance of the IMPs used in clinical trials authorised in their territories,
   - The ethics committees in the protection of clinical trials subjects,
   - The European Medicines Agency in the establishment and maintenance of the EudraVigilance System which includes the EudraVigilance clinical trials module, post-authorisation module, medicinal product dictionary and data analysis system.

ii. There is a need to justify the processing of personal data within the EudraVigilance System for the purpose of safeguarding pubic health while respecting EU data protection legislation.

[a] Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use (ENTR/CT 3)
[b] Detailed Guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module) (ENTR/CT 4).

- A chapter on data privacy should be included in this guidance, similar to the one described under point 20a of the Proposal for a Regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004.

iii. The URL links in foot notes should be checked and updated.

3 Chapter 2.2 – Serious adverse event

3.1 Chapter 2.2.2 – 'Serious event'

- Section 14 is a duplicate of section 12. It could be simplified as followed:

  'An adverse event is serious when it follows the characteristics/consequences defined in Article 2(o) of Directive 2001/20/EC presented above.'

4 Chapter 2.3 – Extended timelines

4.1 Chapter 2.3.1 – Immediate reporting and follow-up report

- The timeline for reporting of all serious adverse events by the investigator to the sponsor should not exceed 24 hours following the knowledge of the adverse event. This is in order for the sponsor to be able to comply with the 7 days expedited reporting requirements if the sponsor then classifies the serious adverse event as a fatal or life threatening SUSAR.

5 Chapter 4.2 – Suspect unexpected serious adverse reaction

5.1 Chapter 4.2.1 – 'Adverse reaction' - causality

- Regarding the reactions associated to non-IMPs detailed in section 28, a cross reference should be added to the first bullet point of Chapter 4.5.

5.2 Chapter 4.2.3 Unexpectedness

- Another section should be added after section 34 to clarify that the definition of unexpected adverse reaction also covers medication errors and the uses outside what is foreseen in the protocol, including the misuse and abuse of the product. This would allow being in line with point 5 of the Proposal for a Directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC.

5.3 Chapter 4.2.4 – SUSARs occurring after the end of the trial

- The investigator should report these reactions without delay to the sponsor who should apply the same reporting obligations than SUSARs occurring during the conduct of the clinical trial. Reference should be made to Chapter 2.3 for the investigator and to Chapter 4.4 for the sponsor.

6 Chapter 4.3 – Assessment of seriousness, causality and unexpectedness

6.1 Chapter 4.3.2 – Causality

1. The Clinical Trials Directive 2001/20/EC defines the obligation of sponsors regarding the expedited reporting of SUSARs. However, in practice, Individual Case Safety Reports (ICSRs) submitted to the NCAs and to EVCTM often also contain events or reactions which do not qualify as SUSAR but which may just be associated to the conduct of the clinical trial or to a non-IMP for which there is no suspicion of interaction with the IMP.

- It should be clearly specified in this chapter that
    - Only cases of SUSARs, for which a reasonable causal relationship between the event and the IMP has been established by the sponsor and/or the investigator, should be reported to the NCAs and to EVCTM,
    - Events with no reasonable causal relationship with the IMP do not need to be reported in the cases of SUSARs (see also to comments on chapter 4.3.3),
    - The causality assessment of the sponsor and/or the investigator should be provided for each reported reaction in relation to any of the suspected or interacting medicinal product.

6.2 Chapter 4.3.3 – Expectedness

1. Section 42 mentions that '*the sponsor is responsible for ensuring that only unexpected adverse reactions are reported.*'
    - It should be specified how to handle expected reactions related to an IMP occurring simultaneously with a SUSAR and which are reported by the investigator in the same case report form. Those reactions provide important information for the analysis of the entire case. Sponsors should be allowed to report the entire information in relation to an individual case (all reactions that occurred in the context of a SUSAR).
2. The conduct of the evaluation of the expectedness by each investigator may lead to a vast disparity of results provided for similar reactions in case of multi-centre clinical trials. This information may also be difficult to obtain within 24/48 hours following the knowledge of the event by the investigator.
    - The assessment of the expectedness of an adverse reaction should remain under the responsibility of the sponsor based on the reference document and its provision should not be made mandatory to the investigator. The section 45 should be deleted or amended as followed:

      'If provided by the investigator, the expectedness assessment should not be downgraded by the sponsor. When the sponsor disagrees with the investigator's expectedness assessment, both, the opinion of the investigator and the sponsor should be provided within the report of SUSARs.'

7 Chapter 4.5 – Adverse reactions not to be reported

1. Regarding the first bullet point,
    - The reference mentioned in the bracket should be changed to
        - The proposed section 52 of Chapter 4.6 as amended bellow in paragraph 8 of this document, and to
        - Section 99 of Chapter 4.11.3.
    - Similarly to the comment above on expected reactions, it should be further specified how to handle
        - Reactions related to a non-IMP, occurring simultaneously with a SUSAR related to an IMP and which are reported by the investigator in the same case report form. Those reactions provide important information for the analysis of the entire case. Sponsors should be allowed to report the entire information in relation to an individual case (all reactions that occurred in the context of a SUSAR);
        - Reactions related to a non-IMP with no suspicion of interaction with the IMP, and which do not occur simultaneously with a SUSAR related to an IMP. In this situation the reporting obligations fall under the provision of Directive 2001/83/EC and Regulation 726/2004 if the non-IMP has a marketing authorisation.

- The Guidance on Investigational Medicinal Products (IMPs) and other Medicinal Products Used in Clinical Trials should be amended to reflect the above discussed recommendations on the handling of reactions related to non-IMP. A reference to this amended Guidance should be added in Chapter 4.5.

2. The second bullet point mentions that there is no need for the sponsor to report SUSARs occurring in a clinical trial performed in the EU for which he is not the sponsor.

   - This is applicable if the SUSARs occurred in a clinical trial which is authorised in the EEA. In the situation where the SUSARs occurred in a clinical trial not authorised in the EEA and for which the main sponsor has no authorised clinical trials in the EEA with the same active substance of the IMP, the "non-sponsor" is the only source of information within the EEA of these SUSARs. He should report them in accordance with Chapter 4.7 and 4.8 when he becomes aware of them. This should be specified in this bullet point.

8 Chapter 4.6 Interface with safety reporting of authorised medicines under pharmacovigilance rules

1. Under section 50,

   - The reference to Volume 9 should be changed to Volume 9A.

2. In section 52,

   - It should be stated that only cases of SUSARs occurring within the context of the clinical trial protocol should be reported in accordance with the Directive 2001/20/EC. This will clarify the situation where the suspected serious adverse reaction is not related to the IMP but is suspected to be only related to a non-IMP with no suspicion of interaction with the IMP. In this situation the reporting obligations fall under the provision of Directive 2001/83/EC and Regulation 726/2004 if the non-IMP has a marketing authorisation. Section 52 could be amended as followed:

     '*An adverse reaction occurring within the context of a clinical trial protocol is only to be reported in accordance with Directive 2001/20/EC and should comply with this detailed guidance.*

     Untoward and unintended serious reactions to a non-IMP, which do not result from an interaction with an IMP, or which are not suspected to be related to both a non-IMP and to an IMP, or which do not occur simultaneously with a SUSAR related to an IMP should be reported in accordance with the applicable pharmacovigilance provisions of Directive 2001/83/EC and Regulation 726/2004 detailed in Volume 9A.'

9 Chapter 4.7 – Reporting of fatal or life-threatening SUSARs to the national competent authority

9.1 Chapter 4.7.1 Initial reporting

1. Under section 60,

   - *'Relevant information'* should be replaced by *'Minimum reporting criteria'* in order to be consistent with the wording in section 56.

   - *'Valid EudraCT number'* should be replaced by *'A valid EudraCT number where applicable, i.e. for clinical trials authorised in European Economic Area or clinical trials which are part of an agreed Paediatric Investigation Plan.'*

   - '*One suspect IMP'* should be replaced by '*One suspect IMP (including active substance name - code)*'

- *'A causality assessment between the SUSAR(s) and the reported suspected/interacting medicinal product(s)'* should be added with the following footnote '*For electronic transmission in ICH E2B(R2): Section B.4.k.18*'

2. It should be mentioned that section 61 refers to the administrative information for electronic reporting. The first sentence could be amended as followed:

   'In addition, in order to properly process the report electronically, the following administrative information should be provided:'

3. Another section should be added after section 62:

   - Reference should be made to Chapter 4.7.4 as regard the format of the report and the structure of the information. The following is suggested:

     'For the format of the report and the structure of the information, see section 4.7.4.'

9.2 Chapter 4.7.2 – Follow-up information

1. The proposed timelines for the reporting of follow-up information regarding fatal or life-threatening SUSARs will disadvantage sponsors who receive follow-up information before the 15 days reporting timeline compared to those who get follow-up information after the 15 days timeline. The management of these 7, 8 and 15 days timelines will be difficult to handle for the sponsors since they will be required to monitor whether the follow-up information has been received before or after the 15 days timeline of receipt of the initial information. In addition the automatic monitoring in EudraVigilance of the compliance of the reporting timelines for the fatal or life-threatening follow-up reports will be technically difficult to implement since this will require additional calculations to assess whether the report has been received by the sponsor before or after the 15 days reporting period of receipt of the initial information.

   - It is suggested to keep the reporting timelines and the text of the answer as outlined in question ID 004 of the Questions & Answers document specific to adverse reaction reporting in clinical trial, Version 1.0 of December 2009 (Doc. Ref. ENTR/F/2/SF/dn D(2009) 40108):

     'If the initial report is incomplete, e.g., if the sponsor has not provided all the information/assessment within seven days, the sponsor should submit a completed report based on the initial information within an additional eight days. In this instance, the receipt date should not be changed with regard to the initial report.

     If significant new information on an already reported fatal or life-threatening case is received by the sponsor, the clock starts again at day zero i.e. at the date of receipt of new information. This information should be reported as a follow-up report within 15 days.'

9.3 Chapter 4.7.3 – Addressee of report, reporting to EVCTM, reporting arrangements

1. The process of improvement of the EVCTM should be more specifically described. Section 73 could be amended as followed:

   'EVCTM will be the transmission tool for reporting of SUSARs to the Member States concerned. To this end, the capabilities of EVCTM will be improved in accordance with section 6.2 of this detailed guidance towards 'enhanced functionalities'. The European Medicines Agency ('Agency'), in collaboration with the Member States and the Commission, shall draw up the functional specifications for EVCTM, together with a timeframe for their implementation. Once the enhanced functionalities have been reached, which will be established by the Commission, following consultation of the Agency and national competent authorities, section 4.7.3.2 will apply. This will be

announced by the Commission. Until that time, i.e. during the transitional period, the reporting modalities set out in section 4.7.3.3 should be followed.'

2. The proposal of direct and indirect reporting detailed in section 75 adds some constraints for sponsors who are running multi-national clinical trials with multiple sites distributed within several Member States.

   - A similar solution as the one detailed in paragraph 2 (b) of Article 24 of the Proposal for a Regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004, could be introduced.
     - In this context, cases of SUSARs would only be directly reported to EVCTM by sponsors. Initial and follow-up reports of SUSARs submitted to EVCTM by sponsors would be transmitted electronically upon receipt to the concerned Member States.
     - The indirect reporting would be limited to sponsors who do not have the resources and experience for direct reporting as detailed in point 76.

3. With reference to the transitional procedures detailed in section 80 and 81, a different option should be proposed for the indirect reporting of SUSARs occurring in third countries. Putting upon the sponsor the responsibility to choose one Member State which would ensure the indirect reporting may lead to situations where the chosen Member State might not have the technical tools to fulfil this task.

   - Instead, the sponsor could be given the option of choosing among Member States, which offer ensuring indirect reporting. However this will still be an issue if the clinical trial has been approved in the EEA by only one Member State which does not have the technical tools to report electronically to EVCTM.

   - For multi-national clinical trials authorised within several Member States, in the option of indirect reporting to multiple concerned Member States, it should be clearly agreed in advance between the concerned Member States, which one will be responsible for the reporting of the third countries cases of SUSARs to EVCTM in order to avoid duplication of reporting to EudraVigilance by several Member States.

4. Section 81 is confusing as it does not clearly mention to which other chapter it is referring.

   - It could be amended as followed, taking into account the proposal discussed above regarding Member States offering ensuring indirect reporting:

     'If the clinical trial is exclusively performed in a third country, the sponsor should report SUSARs referred to in Section 4.4, 2nd bullet directly to EVCTM or choose, after agreement, among the concerned Member States which offer ensuring indirect reporting.'

9.4 Chapter 4.7.4 – Format of report

1. With regard the provision of IMP information in the EudraVigilance Medicinal Product Dictionary (EVMPD), it should be clearly mentioned that this should be done before populating the clinical trial application form for EudraCT.

   - The first bullet point in section 83 should be amended as followed, keeping the footnote as it is:

     'The sponsor should provide information on the investigational medicinal product in the EudraVigilance Medicinal Product Dictionary before completing the clinical trial application form for EudraCT.'

2. Complimentary to the information provided for free text fields, a reference to the use in coded fields of internationally agreed terminologies, formats and standards should be included.

   - The following paragraph should be added after the second bullet point in section 83:

     '*The data in coded fields should contain internationally agreed terminologies, formats and standards for the conduct of pharmacovigilance.'*

3. It should be emphasized that cases which do not meet the minimum requirements detailed in the current version of the *Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)* will not be accepted by EVCTM.

   - The following should be added as bullet point in section 83:

     '*Only reports complying with the validation rules (mandatory fields and business rules), as detailed in the current version of the Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual case Safety reports (ICSRs) (Doc. Ref. EMA/20665/2004/Final)*[c] *will be accepted in EVCTM.'*

4. Reference to data quality assurance and quality control as addressed in Chapter 10.7 of the Detailed Guidance ENTR/CT 4 should be maintained in the revised Guidance. This is a critical point, which needs to be addressed when submitting cases of SUSARs. In addition detection and management of duplicated individual cases should also be taken into account.

   - The following paragraph should be included as bullet point in section 83:

     '*It is the responsibility of the party making the data submission, coding or entry to ensure accuracy and completeness of the case at the time it is first submitted to EVCTM. The detection of duplicated individual cases should also be addressed. Staff responsible for data submission, validation, entry and review should be trained for the purpose and have standard operating procedures available to them. Quality control and assurance systems should be in place to verify the accuracy and integrity of the data entry.'*

10 Chapter 4.9 – Reporting of SUSARs to Ethics Committees and Chapter 4.10 – Informing the investigator

1. These two chapters should be extended:

   - This is to allow for clarification as regards which type of SUSARs should be submitted to the Ethics Committees and to the investigators. Particularly it should be specified:

     - Whether this reporting concerns all types of SUSARs related to the active substance of the IMP of the concerned clinical trials and for which the sponsor becomes aware of,
     - Or if it is limited to SUSARs which occur
       - In the concerned clinical trial or
       - Only in the country where the clinical trial is authorised (for multinational clinical trials).

2. Chapter 4.9 covers the reporting of SUSARs to Ethics Committees, but also refers to section 4.7.4.2, where it is stated that '*the information should follow the structure as provided for direct submission in order for the national competent authority to enter the data in EVCTM*'.

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[c] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800250b3

- Does this mean that reporting to the Ethics Committees should be done in ICH E2B(R2) format?
- The possibility of submitting line listing should also be provided for informing the Ethics Committees.

3. In the last sentence of Chapter 4.9:
   - The word '*event*' should be replaced by '*reaction*' since it refers to SUSARs reporting and not events.
4. Chapter 4.10 refers to the format for informing investigators about SUSARs and allows aggregated data to be presented as line listing. Currently local law in several countries request single cases to be sent to the investigators.
   - The text should clarify whether line listings will be systematically accepted, providing they are accompanied by a concise summary of the evolving safety profile of the IMP.
   - As highlighted during the European Commission - European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future' of November 2007, investigators are overloaded with individual reports of SUSARs. It would be more relevant to recommend the submission of line listing rather than individual reports. Section 91 should start with

     'Whenever possible, the information on SUSARS should be aggregated in a line listing of SUSARs…'
   - A maximum period covered by the line listings should be indicated in this guidance as well as the timeframe for submitting them to the investigators.
   - The text should specify how to report the SUSARs in line listings in case of blinded trials and a cross reference with Chapter 4.11.1 should be included. It is proposed to keep the wording of Chapter 5.3 of the current guidance ENTR/CT3:

     '*In the case of blinded trials (see section 4.11.1) 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.'*
   - The notification of important significant safety issues by the sponsor to the investigators as detailed in the current guidance ENTR/CT 3 should be maintained. The following is proposed:

     '*If a significant safety issue is identified, either upon receipt of an individual case report or upon review of aggregated data, the sponsor should issue as soon as possible a communication to all investigators. This is applicable as well for a safety issue which impacts on the course of a clinical trial or development project.'*

11 Chapter 4.11 – Other issues

11.1 Chapter 4.11.1 Blinded IMPs

1. It should be clearly mentioned that as a general rule only un-blinded SUSARs should be reported to NCAs and EVCTM.
   - The following sentence should be added at the end of section 94:

     '*As a general rule only un-blinded SUSARs should be reported by the sponsor to the NCAs and to EVCTM.'*
2. '*Investigators'* should be deleted of the last sentence of section 94 in order to be consistent with the second sentence of the same section where it is mentioned that '*the*

blind should be maintained for persons responsible for the ongoing conduct of the study (such as the study management, monitors, investigators)…'

11.2 Chapter 4.11.2 – SUSARs associated with active comparator or placebo

1. A reference to Article 2(d) of the Directive 2001/20/EC should be added in the first sentence of section 98.

11.3 Chapter 4.11.3 – Safety issues not falling within the definition of SUSAR – other follow-up measures

1. Reference is made in section 100 to Chapter 3.A.2 of ICH E2A which provides examples of safety issues not falling within the definition of SUSAR such as

   - An expected serious reaction for which an increase in the rate of occurrence is judged to be clinically important.
   - A significant hazard to the patients population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
   - A major safety finding from a newly completed animal study (such as carcinogenicity).

   The guidance should specify that these safety issues should be subject to immediate reporting to the concerned NCAs, since they may jeopardise the safety of the clinical trial subjects. Information on the format to submit these safety reports, which was included in Chapter 5.1.6.4 of the Detailed Guidance ENTR/CT 3, should also be provided in this guidance.

12 Chapter 5 – Yearly reporting of suspected serious adverse reaction by the sponsor

1. The guidance introduces the Development Safety Update Report (DSUR) that should replace the Annual Safety Report when the ICH E2F guideline is published and implemented.

   - On that point, it is suggested:
     - To organise a centralised declaration of the Development International Birth Date (DIBD), and to give further details on when (at the time of the clinical trial application), by whom (sponsor) and how (EudraCT or other repository) the DIBD has to be notified.
     - To organise a single European electronic repository of DSURs in order to simplify the reporting and assessment processes.
   - In this aspect, reference is made to the similar proposals which are made in the post-authorisation phase,
     - For the Periodic Safety Update Report (PSUR), in Article 25 (a) of the Proposal for a Regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004,
     - For the Community Reference Date, in point 7 of Article 107 (c) of the Proposal for a Directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC.

13 Chapter 6.3 – Enhance functionalities

1. The enhanced functionalities will require the implementation of a regular exchange of data between EudraCT and EudraVigilance database.

- The first sentence in section 109 should be amended as followed:

  'After the transitional phase (section 4.7.3.3), EVCTM will have the following enhanced functionalities based on regular exchanges of data with the EudraCT database.'

2. In point (1), EV-CTM should be replaced by '*the EudraVigilance Data Analysis System'*
3. In point (3), *'ICH'* should be included before *'E2B'*
4. The following sentence should be added at the end of Chapter 6.3:

   'Any substantial change to EVCTM and to the functional specifications should take into account the recommendation of the Member States.'