September 2010

Submission of comments on the 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').

Comments from:

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1. General comments

General comments	Outcome (if applicable)
EuropaBio welcomes the opportunity to input into the European Commission consultation on the proposed revision of the detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use ('CT-3'). Overall, we believe the draft detailed guidance is a solid and useful piece of work, and we particularly welcome the attempt to streamline expedited safety reporting using EudraVigilance. We strongly recommend that member state specific requirements for SUSAR reporting should be made available at EU level. Our comments below represent the feedback from member companies. We hope that the following related issues will be addressed by the Commission when finalising the guidance. We are surprised to see that periodic reporting of SUSARs to Ethics Committees by the sponsor has been deleted, with all SUSARs now required to be expedited. This would seem to be a retrograde step as Ethics Committees have been requesting sponsors to report foreign SUSARs periodically and we would therefore request clarification on this issue. We are also concerned that a new requirement for investigators to assess 'expectedness' (currently performed by the sponsor) has been introduced. This will place additional workload on both investigators and sponsors and require extensive system changes for no apparent gain. For international clinical trials, taking place in the EU as well as outside the EU, the guidance should clarify when to start ex-EU SUSARs reporting to Member State and to EudraVigilance (e.g. on approval of the trial by the first Member State). It would also be helpful if the guideline addresses the need of sending as "backlog" the ex-EU SUSARs of a clinical trial generated prior to first approval in the EU.	

General comments	Outcome (if applicable)
Following the publication of the revised detailed guidance on clinical trials, CT-1, the end of trial notification is not required at national level. This notification was previously used to stop safety reporting at Member State level. It is now unclear if safety reporting, expedited and periodic has to be maintained to all concerned Member States and EudraVigilance until the worldwide end of trial notification, leading to unnecessary burden for sponsors and competent authorities. Furthermore, the draft revised guidance implies that a SUSAR is per definition arising from a clinical trial conducted in the EU. This is confusing since there are also reporting requirements for serious unexpected spontaneous cases from third countries if the product is not approved in the EU whilst studies are conducted in the EU. Finally, the Clinical Trial Facilitation Group (CTFG) is working on a work-sharing exercise for assessing Annual Safety Reports (ASR/DSUR), and we believe it would be suitable if this guidance should include the outcome of this exercise; ideally leading to the submission of one single ASR/DSUR sent to one central repository accessible to all concerned competent authorities and ethics committees.	

2. Specific comments on text

Guideline section	Comment and rationale; proposed changes	Outcome
Section 2.2 Paragraphs 12 and 13	We propose to start this paragraph with the definition of "adverse event" followed by the definition of "serious adverse event".	
Section 2.2 Paragraph 16	We propose to include examples for "important medical events", such as events related to the study procedure, incident or near-incident that could lead to serious safety issues for cell-based products and tissue engineering products.	
Section 2	We propose to include a section on "assessment of causality" in section 2 relating to the investigator's responsibilities. This should include the causality assessment with the IMP but also (when applicable) with the study procedure, and the procurement, preparation, manufacturing, storage, injection for cell-based and tissue engineered products. We also propose to add a section on "case identification". The investigator should clearly identify in the report each safety case (whether initial or follow-up report) so there is no misunderstanding between all follow-up reports received for the same patient.	
Section 4.2.1 Paragraph 28 and Section 4.5 paragraph 48	There is cross reference to section 4.2.1 which does not actually give guidance on how to report such non-SUSARs. The section where some guidance is provided is section 4.11.3. The various options provided may not be appropriate for some individual SUSAR reports, e.g. for a non-IMP. The document also remains silent regarding the current provision for a sponsor to report spontaneous SUSARs from third countries where the IMP is marketed and which is still in the pre-authorisation phase in the EU. It is unclear if this was an inadvertent oversight or if such cases would now not be considered SUSARs. In addition, SUSARs occurring in an EU clinical trial are unlikely to come to the knowledge of another sponsor undertaking trials with the same IMP through spontaneous reporting. We propose that paragraph 48 cross refers to section 4.11.3 as this section is more	

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	relevant, while paragraph 101 is expanded to give guidance on how to report non-SUSARs from a solicited (interventional) source but which are not of sufficient concern to warrant an urgent safety restriction, termination of the trial or a substantial amendment to the protocol. For example, it may be appropriate to send a copy of the non-SUSAR report to the manufacturer of the non-IMP. We also propose to include in paragraph 48 an additional bullet point which covers SUSARs from spontaneous sources where an IMP is marketed in a third country by the sponsor but not yet authorised in any Member State. We suggest rewording as follows: 48. It follows from section 4.4 that there is no need for the sponsor to report : • Adverse reactions not related to the IMP… This is addressed through the reporting and follow up measures outside SUSAR reporting (see section ~~4.2.1~~ **4.11.3**); or • SUSARs occurring in a clinical trial performed… These SUSARs may come to the knowledge of the sponsor through publications (such as academic literature) or regulatory authorities • **SUSARs from spontaneous sources where an IMP is marketed in a third country by the sponsor but not yet authorised in any Member State** **4.11.3. safety issues not falling within the definition of SUSAR – other ~~follow up~~ measures** 101. These events/observations are not to be reported as SUSARs according to this detailed guidance. However, these events/observations may require other action during a clinical trial which may require action such as: • **Notification of individual serious and unexpected ADR reports which do not qualify as SUSARs, e.g., from non-IMPS to the original marketing**	

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	authorisation holder	
Section 4.2.4	The obligations related to the management of SAEs related to a clinical trial do not finish with the end of the trial. However, we do not understand the obligation of reporting SUSARs after the end of trial in a concerned MS when no more patients are being treated with the product in this MS. The fact that the end of trial notification at the national level was removed in the revised CT1 guidance generates concerns that the expedited and periodic reporting in the EU for international clinical trials could be required until the worldwide end of trial notification regardless the fact that no more patients are being treated in the EU. In any case should the sponsor submit a national end of trial notification, this should then remove the obligation for SUSAR reporting. Exceptions should be foreseen in case of post-end-of-trial safety issues that would require trial subject information and medical follow-up due to the participation in the trial.	
Section 4.3.3	We propose to add a statement about expectedness for events related to study procedure and incident/near-incident: expectedness for serious adverse reaction related to study procedure and incident/near-incident should be all considered as unexpected unless otherwise specified in the protocol.	
Section 4.3.3 Paragraph 45	We note the introduction of a new requirement for the sponsor to obtain an expectedness assessment from the investigator for all serious suspected ADRs. Member companies expressed concerns about this. We do not see a public health justification for changing this notion of separate determinations by sponsor and investigator. There should be no difference between sponsor and investigator determination of expectedness and this new provision seems to legitimise the thinking that there could be a difference. If an investigator does not provide a determination of "expectedness," would the sponsor's assessment be the final one plus an ongoing query? Otherwise, if a "blank expectedness" per investigator defaults to "unexpected," there would be a tremendous over-reporting of	

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	SUSARs. This is very different from "blank causality" per investigator. This will lead to confusion. The sponsor is in the best position to determine expectedness reliably and within the timelines. The Investigator makes his or her judgement based upon sponsor-supplied information and hence repeating the analysis of the sponsor by the investigator will lead to confusion. In addition: • This section conflicts with the guidance provided in section 4.2.3 (34), which states that "The unexpectedness of an adverse reaction is determined by the sponsor according to the reference safety information." • The sponsor is in a better position to understand the regulatory meaning of expectedness than the investigator, who is more likely to use their medical judgment of the patient's condition, disease and expected pharmacological effects of the IMP as opposed to what is in the reference safety information. • Practical issues in training and retraining all investigators every time the reference safety information is updated. • There are also concerns about consistency among investigators, and the fact that none of the internationally-accepted consensus guidelines (e.g., ICH or CIOMS) include the concept of investigator-supplied expectedness assessments. • It would appear that sponsors will need to record both investigator and sponsor opinion of expectedness. If this is the case, this will impact systems considerably (e.g., an additional data field not currently specified amongst the E2B electronic case reporting data elements). We strongly recommend that paragraph 45 is deleted.	
Section 4.4 Paragraph 46	We suggest including a definition of 'third country' in section 1.3	

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Section 4.4 Paragraph 46 2nd bullet	Clarification is sought on the requirements regarding the beginning of reporting obligations. What are the reporting requirements for SUSARs related to the same active substance that occurred before EU approval during clinical trials performed only in non-EU countries: should SUSARs be reported as back-log reports as soon as a clinical trial with the same active substance is approved in the EU? What are the reporting requirements for SUSARs occurring in the clinical trial in a non-EU country during evaluation of the CTA in the EU: should SUSARs be reported as back-log reports as soon as the clinical trial is approved in the EU? This situation is not described. Likewise clarification is required regarding the SUSARs occurring in a clinical trial performed in a third country and in EU Member States.	
Section 4.4 Paragraph 46 and Section 4.7.3.3 Paragraph 78	The final point on page 7 refers to SUSARs to be reported from trials "sponsored by another sponsor who is either part of the same mother company or who holds a development agreement with the sponsor". This does not encompass the complexity of business development agreements and introduces the potential for duplicate reporting. We suggest rewording as follows: - sponsored by another sponsor who is part of the same mother company or **as stipulated in the safety data exchange agreement which must ensure that one party takes responsibility for notification of SUSAR**s. The same proposed change would also apply to the second point in paragraph 78.	
Section 4.6 Paragraph 50	Footnote "13" should provide the link to volume 9a instead of volume 3	
Section 4.7.1.2 Paragraphs 60/62	Valid EudraCT number: We suggest adding "when applicable" to take into account non EU clinical trials. One identifiable reporter: The qualification of the reporter should be addressed in the document. Should the reporter be a healthcare professional? If not, does a case need to be	

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	medically confirmed by a healthcare professional in order to be processed?	
Section 4.7.2.1 Paragraph 63	"Within an additional eight days": We believe that this should be from the date of receipt of the new information to allow the sponsor to process and prepare the report.	
Section 4.7.3.2 Paragraph 75	This section provides the option of either direct or indirect reporting to EVCTM, as determined by the Member States. In these circumstances : • It is inevitable that different Member States will oblige different options, in which case, for any multinational trial, sponsors would be submitting directly to EVCTM for some countries but not others. • As Member States can oblige either direct or indirect reporting, it is difficult to see how the third option (leaving the sponsor to choose) can actually work for a SUSAR occurring in a Member State in which the competent authority obliges the route of reporting which is not the sponsor`s choice. • As a practical matter, direct reporting would be the only option for third country SUSARs as, if many sponsors choose Member States which ensure indirect reporting, this would place an undue burden on the competent authorities concerned. As a result, not only will complex procedures need to be put in place by sponsors (particularly for multinational trials) but there is the added problem that, if sent directly to EVCTM by the sponsor, the ICSR could then be duplicated by another competent authority which chose indirect reporting, especially for third country reports. We believe only one route for reporting should be available. Our preference is for direct reporting by the sponsor as this is consistent with the proposed new pharmacovigilance legislation for spontaneous report submission to EVPM and allows for a single process for multinational studies. In particular, we consider that direct reporting should be mandatory for third country SUSARs.	

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	We suggest revising paragraph 75 as follows: Reporting Modalities and Use of the European database – direct **~~and indirect~~** reporting As regards the input of information regarding SUSARs into EVCTM, Member States may: • **Oblige** the sponsor to report directly as individual case safety report (ICSR) to EVCTM only (hereafter referred to as direct reporting). The national competent authority of the Member state concerned is then informed through EVCTM	
Section 4.7.3.3 Paragraph 77	Some Member States issue exemptions for SUSARs reporting (reporting to EVCTM only) or only want to receive local SUSARs. Not all SUSARs referred to in section 4.4, 1st bullet, need to be reported to every Member State concerned. This should be clarified in this paragraph.	
Section 4.9 Paragraph 89	SUSARs reporting to ECs should be under CIOMS I format in English. This should be clarified in this paragraph. Rather than sending expedited reports to the concerned ECs (i.e. where the event occurred), we propose to send to the concerned EC only the safety urgent issues and aggregated information (line listing) submitted to the investigators in periods as warranted by the nature of the clinical development project. We would also recommend for the ECs to be integrated into the EV Community in order to allow electronic reporting to ECs as well as to competent authorities.	
Section 4.10 Paragraph 91	This paragraph appears to give a much welcomed flexibility regarding the sponsor communication with investigators. It would be additionally helpful to provide a more defined guidance on the appropriateness (e.g. urgent safety measures) and periodicity of the line listing for the investigators. Should this be a sponsor decision, the sponsor judgement should then be accepted by the	

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	competent authorities. We propose to update paragraph 91 as follows: If appropriate, the information on SUSARs should be 1) blinded unless judged non-appropriate by the Sponsor for safety reasons and 2) 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 as solely assessed by the Sponsor.	
Section 4.11.1 Paragraph 94	The following statement "The blind should be maintained for persons responsible for the ongoing conduct of the study (such as the study management, monitors, investigators) and those responsible for data-analysis and interpretation of results at the conclusion of the study, such as biometrics personnel" is stronger than in the previous version, which said this was recommended where possible. We note that maintaining the blind for persons responsible for the ongoing conduct of the trial is not always possible, as investigators want to know whether an individual patient who may be compromised is on a placebo or the IMP, usually they keep notes on these findings, and these notes are read by study monitors. We recommend using the conditional statements in the former version. The unblinding process should capture the concepts in the ICH E2A guideline. In addition, the last part of the last sentence could be misinterpreted as allowing all investigators access to all unblinding information. We suggest revising as follows: 94. **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**	

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	concerned Member State. The blind should be broken only for that specific patient by the sponsor. Unblinded information should only be accessible to those who need to be involved in the safety reporting to EVCTM, national Competent Authorities, ethics committees, and Data Safety Monitoring Boards, or persons performing ongoing safety evaluations during the trial. **Investigators may have access to unblinded information if directly pertinent to assure the safety of individual clinical trial participants. The blind should be maintained for other investigators and for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion.**	
Section 4.11.1 Paragraph 96	In practice, it is difficult to have the DSMB composition and operation integrated in the protocol as the DSMB Charter is usually validated during the first DSMB meeting (i.e. far after the protocol finalisation). We then propose to state that the DSMB Charter, compliant with available guidelines, will be included in the Trial Master File once it is finalised.	
Section 4.11.3	We understand here that events related to study procedure, product preparation/procurement etc., are not considered as SUSARs. This is not in line with some Member States current requirements asking for cell and tissue-based product incident/near-incident with potential safety impact to be reported as SUSARs using a CIOMS I form or considering safety issues related to clinical trial specific procedures as SUSARs.	
Section 5	Annual safety reports for first-in-man trials and subsequent short term metabolism or pharmacokinetic studies are no longer mentioned in the CT-3 guidance - they also do not appear in the draft ICH E2F. Clarification on what should be reported and timelines to report should be provided in one of these two documents.	