EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

07 Sept 2010

# Submission of comments on '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:** European Quality Assurance Confederation (EQAC)

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

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# 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)<br>*(To be completed by the Agency)* |
|---|---|---|
| | The current guidance specifies that "The sponsor is responsible for the ongoing safety evaluation of the investigational medicinal product(s)."<br>This was used by inspectors to justify the need for some signal detection approaches during clinical development. This is now omitted in the draft revised guidance, which may suggest that the sponsors are not expected to perform any signal detection during clinical development. It would appear relevant to include a requirement for signal detection during Clinical Development. | |
| | Why can't this be transferred to Regulation? If this document remains a Directive it will still allow the Member State CAs to apply it as they wish to their own territory and their own legislation. We have seen this happen with 2001/20/EC and this Detailed Guidance. There is currently no harmonisation as prescribed within 2001/20/EC because the Agency and Commission appear unwilling to force the point. The single result of this is inefficiency, confusion, over reporting of SUSARs, and poorly delineated responsibilities. This revision will not help matters whatsoever. | |

## 2. Specific comments on text

| Paragraph(s) of the relevant text | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
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| 18 | | It would appear more appropriate to systematically specify those events that do not require immediate reporting in the protocol, and therefore we would propose to remove the reference to the IB. | |
| 19 | | The existing standard in the industry for reporting SAEs by the investigator to the sponsor is "immediately within 24 hours". The choice of a 48h timeline therefore appears inappropriate. | |
| 20 | | *"The follow-up report should allow the sponsor to assess in detail whether the adverse event requires a reassessment of the risk-benefit balance of the clinical trial"*<br>What will be the corresponding expectations to satisfy this point? It could be interpreted that the investigator will be expected to make a statement that a report does not need such reassessment, which would be applicable for most cases and create an additional burden for little benefit.<br>This paragraph should be clarified or removed. | |
| 2.3.2. | | *Non-immediate reporting*<br>We would suggest to keep this simple and refer to the study protocol for the reporting of all other Adverse Events. We would propose to remove the reference to the IB. | |
| 36 | | *"The sponsor is responsible for ensuring that the reported reaction is serious."*<br>It would be useful to include some guidance regarding the possibility that the sponsor disagrees with the investigator on Seriousness, i.e. is it acceptable for the sponsor to downgrade seriousness, or is it not (like for causality – see § 41).<br>It should be clarified that it is the sponsor's responsibility to assure that the Investigator has applied the criteria for seriousness correctly. It may also say how the sponsor should do this. e.g. training of the Investigator and as early in the process as possible. | |

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| 37 | | This statement is confusing: All AEs (via CRF) and SAEs should be reported to the Sponsor whether or not a causality assessment is provided by the investigator. | |
| 40 | | "The assessment of causality is often made by the investigator"<br>We would propose: "the investigator shall always provide a causality assessment and it is the sponsor's responsibility to make sure that this is done". | |
| 41 | | It may be considered to clarify that the absence of causality assessment by the investigator should not imply causality, i.e. in this case the assessment by the sponsor should prevail until follow-up information is obtained. In the absence of guidance, it is currently a common approach to assume causality if not provided by the investigator, which results in over-reporting. | |
| 45 | | Expectedness:<br>The draft revision suggest a significant change in current arrangements with the involvement of the investigators in expectedness assessment. It is unclear that this would bring any benefit. This is already a rather subjective assessment which leads to some inconsistencies within and between companies, and it cannot be ascertained that investigators have sufficient training and understanding of Pharmacovigilance principles to perform such assessment, not to mention the additional capacity required.<br>In a context where this variable may be taken out of future requirements with the possible reporting of all SSARs, this new provision is not considered appropriate and we would suggest to remove §45. | |
| 45 | | Like for causality, it may be considered to clarify that the absence of expectedness assessment by the investigator should not imply unexpectedness, i.e. in this case the assessment by the sponsor should prevail. | |
| 46 | | SUSARs to be reported:<br>The draft revision now excludes one category of SUSARs from the reporting obligations to individual member states (i.e. | |

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| | | those occurring in separate trials taking place in other Member States). While this new set of rules implies a lower volume of SUSARs to be submitted to individual member states, it brings a new level of complexity and an associated risk of non-compliance. It will probably appear easier to commercial sponsors to abide to current rules and over-report.<br>The benefit of this new set of rules is also very questionable in terms of patient protection. It should rather be considered to adopt the approach currently applied by many Member States, i.e. all SUSARs to EudraVigilance +/- Local SUSARs to individual Member States. | |
| 46 | | Second bullet point:<br>What is understood by "*a development agreement with the sponsor*"?<br>Would this include academic studies somehow supported by the sponsor (i.e. Investigator-Sponsored Studies where the sponsor provides some type of support, e.g. financial) ? Or does this type of SUSAR fall under the second bullet point of 4.5 ?<br>It should be considered to clarify this. | |
| 48 | | Should avoid referring to 'outside SUSAR reporting'. Should refer to Directive 2001/83/EC and Regulation 726/2004 and to section 4.6. | |
| 49 | | There is use of the phrase 'pharmacovigilance of authorised products' in paragraph 40 with the intention to exclude adverse events associated with the IMP. However, it is possible to run clinical trials using authorised products. This need to be written more clearly. | |
| 52 | | As it stands at the moment paragraph 52 is inaccurate and confusing. It should be stated more clearly so as to emphasise that it refers to adverse events associated with the use of the IMP whether the IMP has a marketing authorisation or not. | |
| 54 | | This is a copy/paste of the directive which does not help. Typically the sponsor submits in parallel to EV plus the national CA (i.e. MS in whose territory the event occurred). | |

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| | | Some member states only require direct reporting to EVCTM, which is the type of guidance one would expect in this document. | |
| 57 | | This would needs to reflect the Vol 10 Q&A documents to avoid any ambiguity and conflict regarding "relevance" – see question ID002. | |
| 63 | | 4.7.2.1. Timelines (1)<br>Follow-up information received before the 15 days reporting timeline" should be changed to "(1) Follow-up information received after day 0 and up to and including day 15, reporting timeline". | |
| 66 | | If information is not obtained within the additional 8 calendar days this new statement may open up less scrupulous sponsors to simply be more relaxed about obtaining follow-up and wait until the 8 calendar days have expired and have more time to submit with the resetting of the clock. | |
| 71 | | This may not be consistent with what some Member States currently require (see paragraph 54). | |
| 4.7.3.2 | | The reporting route for SUSARs is confusing. The transitional arrangements are not clear | |
| 4.7.3.2. | | Reporting modalities and use of the European database – direct and indirect reporting:<br>It would be a shame not to use this opportunity to harmonize the flow of information. Direct reporting would appear desirable and would harmonize the reporting process with the planned process for Post-Marketing. It would also simplify the rules for reporting as paragraph 46 could then be simplified (i.e. All SUSARs to EudraVigilance).<br>The proposed revision also generates a potential for conflicts in multinational trials if separate Member States chose different procedures, which may also vary | |

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| | | between trials in the same development project, or between projects, which could result in great confusion to the detriment of patient safety.<br>The approach of the MHRA is illustrating this potential issue: All UK and third country reports submitted via the MHRA's new eSUSAR website will be forwarded to the EVCTM (http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm), which will result in all third country reports being reported as duplicates to EVCTM if other Authorities follow a similar approach. | |
| 4.7.3.3. (2) | | Transitional reporting procedures to EVCTM:<br>The provisions of paragraphs 79, 80 and 81 do not promote harmonisation. It should be considered to simplify this and require the sponsor to submit all SUSARs to EVCTM, which appears to be the arrangement currently applied in all Member States. | |
| 89 | | 4.9. Reporting of SUSARs to Ethics Committees:<br>This is an aspect that is causing confusion due to the lack of harmonisation and excessive volume of reporting to Ethics Committees who cannot interpret the information submitted. The draft revision is even less clear than the current guidance with regards to the selection of SUSARs that qualify for reporting to Ethics Committees. It could be understood that the same cases should be expedited to Competent Authorities and Ethics Committees, which would be more than what is currently done. The possible use of periodic Line-Listing as per the current guidance is no longer mentioned which appears surprising. | |
| 91 | | Informing the investigator:<br>The draft revision brings a lot of flexibility in the existing arrangements and it should be considered to set a | |

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| | | minimum frequency (e.g. every 6 months). With the proposed wording, it could be understood that it may be appropriate not to send any information to the investigators, e.g. for relatively short trials or low SUSAR Volume, which could make it very difficult to verify compliance. | |
| 91 | | Informing the investigator:<br>The draft revision does not specify whether the information provided should be blinded. | |
| 94 | | *"The blind should be maintained for persons responsible for the ongoing conduct of the study"*<br>The category of personnel concerned has been extended to include the study management, monitors, investigators, in addition to those responsible for data-analysis and interpretation.<br>This seems to contradict ICH E2A (D) which states: *"breaking the blind for a single patient usually has little or no significant implications for the conduct of the clinical investigation or on the analysis of the final clinical investigation data"*.<br>The respect of this rule requires very complex arrangements to ensure that Competent Authorities and Ethics Committees receive unblinded information, while others receive blinded information (e.g. Investigators). By experience, these arrangements often fail to reach their objectives because at some place in the organisation, a sponsor representative gets involved with the reporting of unblinded SUSARs to Ethics Committees. This can also happen through the reporting of DSURs, which should contain the information about unblinded SUSARs.<br>In addition, even though the Investigators listings are supposed to be blinded (which is not specified in paragraph 91), it may be relatively easy to derive the treatment allocation from the information provided.<br>Some companies have adopted the policy whereby no effort is | |

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| | | made to keep anyone blinded to SUSARs, but measures are implemented to ensure that this does not generate bias in the analysis of the study results. This approach appears acceptable and should possibly be presented as an option in the guidance. | |
| 98 | | This paragraph makes little sense in reference to placebo reporting: the investigator provides a causality assessment to the unblinded IMP. If the event is unexpected, the blind is broken and the patient was administered placebo, we have a SUSAR but no information from the investigator whether the event could be associated to an excipient or impurity. These cases should not warrant submission but most companies submit because only a single investigator causality assessment was provided. Wording in paragraph 98 would need to be clarified to avoid this situation of over-reporting. | |
| 99 | | Submissions of SUSARs associated with Non-IMPs remains ambiguous (see also paragraph 28). There is no mention of reporting these to either EVCTM or to the manufacturer if known, which could result in the loss of potentially important safety information. It should be clarified that the rules for spontaneous post-marketing reporting apply (this could also be mentioned in 4.6). | |
| 100 | | Other safety issues requiring expedited reporting:<br>This section from the current guidance has been removed. One of the examples given is "*a serious adverse event which could be associated with the trial procedures*". This was introduced with the EU Guidance and led Sponsors to collect SAEs from the time the patients signed their consent, as opposed to when the IMP was administered, so that events related to trial procedures could be collected, including wash-outs or invasive procedures. As this is now omitted in the draft revised guidance, should the sponsors start revise their procedures and only collect SAEs after the IMP is administered ? | |

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| Section 6 | | The relevance of this section is questionable. It seems misplaced and should really be added to the EudraVigilance documentation and not to this Detailed Guidance. Functionalities of the EVCTM should be an appendix. There is no description of procedures or timing of when things should be done to assist in the collection, verification and presentation of adverse events to aid the collection, verification and presentation of adverse events. (See Introduction 1.1.2 on the purpose of the guidance document). The problem is that the reader would spend a lot of effort reading these paragraphs trying to understand what they should be doing and when they should be doing it. | |

Please add more rows if needed.