Submission of comments on 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')

Comments from:

Name of organisation or individual
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1. General EFPIA Comments

General Comment	Proposed Amendment
EFPIA welcomes this initiative by the European Commission to provide simplification and further clarification of a number of previously ambiguous sections of the existing detailed guidance, in particular: • Introduction of the need for all national requirements to be consistent with procedures and timescales in Directive 2001/20/EC • Clarification of the interface with safety reporting of authorised medicines under PV rules • Clarification of Day 0 and consistency with the clock start for spontaneous reports The drive to reduce bureaucratic burden to allow sponsors and other important stakeholders to focus effort and resource on patient safety is clearly supported. Nevertheless, as detailed further below, EFPIA are very concerned that the currently proposed version of the detailed guidances has now been amended to the point where it is more difficult to read and considerably less useful to sponsor than the current ENTR/CT3 of April 2006. This will lead to more ambiguity and potential for differing interpretation by all stakeholders (including the Competent Authorities). We therefore consider that the existing guidance should be used as a basis for the revision, with a focus on sections where changes are considered necessary. If this is not possible, then we recommend that extensive rewriting of the currently proposed document is needed in order to generate a detailed guidance which is useful to sponsors and all stakeholders. (as indicated in our subsequent comments)	

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As already highlighted, in streamlining the guidelines, EFPIA notice that either previously useful detail has been removed or a considerable degree of cross reference to other documents has been introduced (e.g. ICH E2A and within the document itself). This results in a document which is : • somewhat inconsistent in places as there are other sections which contain the full content of the relevant section of the referenced document or full definitions (e.g. definitions of serious and unexpected) • less useful than the previous guideline in some sections which have been significantly shortened e.g. unblinding procedure is now omitted • less user friendly as the reader either has to frequently cross refer to a completely different document or regularly need to change pages in order to cross refer to other sections of the guidance. We also consider that inclusion of definitions within the text of the document makes the document less easy to follow than having all the definitions collated in an annex (as per the current guideline) • introducing increased complexity in what should and should not be reported on an expedited basis. This will undoubtedly compound the existing inconsistency in implementation across the Member State Authorities. EFPIA therefore proposes that, wherever feasible and practical, the number of cross references is reduced and full explanations/definitions are provided in as far as they can be readily "cut and pasted" from the original reference documents. We also recommend that all the definitions and corresponding comments are removed from the body of the guidance and collated into an Annex. In addition, inclusion of a simple table clearly and concisely summarising expedited reporting requirements would help reduce confusion and minimise the potential for inconsistent interpretation.	The sections to which these recommendations apply are as follows : • 1.2 (5) – Scope of the guidance • 1.3 - Definitions – Move to an Annex • 2.2 – Definitions – Move to an Annex • 2.2.2 (17) – quote full examples from ICH E2A • 3 (23) Regarding the definition of adverse event, reference is made to ~~section 2.2.1~~ Annex xxx • 4.2 Definitions – Move to an Annex • 4.2.3 (34) – include reference from CT -1 • 4.3.2 (39 and 40) – include full ICH E2A reference • 4.7.3.3 (77) Transitional Reporting procedures – give the full details of the SUSARs from section 4.4 (first and second bullet points) • 4.11.1 Blinded IMPs – reinstate the unblinding procedure form the current detailed guidance • 4.11.3 (100) – include full ICH E2A reference • Add a table which concisely and clearly summarises expedited reporting requirements

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EFPIA note that a former provision in the existing guidance in relation to reporting of SUSARs to Ethics Committees has been removed in this draft (namely to allow sponsors to send periodic line listings to Ethics Committees in addition to national SUSARs). We understand the rationale for this as it is at variance with the current Directive 2001/20/EC. Equally, however, it is clear from various Ethics Committee member comments and the Ethics Committees representatives at a joint EU Commission/EMEA consultation meeting held in October 2007, that they consider that they are receiving too much information in a non –concise form which often leads to data overload and the loss of relevant safety signals. This can ultimately undermine the role of the Ethics Committees in patient-safety protection. Strictly applying the provisions for submitting individual SUSARs to Ethics Committees (as outlined in Article 17 of Directive 2001/20/EC) will therefore not address this significant concern. Furthermore, sending individual SUSARs to Ethics Committees as opposed to national SUSARs and periodic line listings will create additional bureaucratic burden for sponsors who have utilised this process for many years with no apparent negative impact on study subject safety. EFPIA fully appreciates that the detailed guidance cannot conflict with the provisions of the CT Directive itself but is nevertheless concerned by the increased burden on both stakeholders when there is no ostensible benefit to patient safety. EFPIA had considered a number of different proposals for amendments to the current draft guidance to rectify this situation but, as these would all require a change in the current legislation, we would like to use this opportunity to propose (as invited by the Commission) that provision for periodic notification of SUSARs should be included in the future revision of Directive2001/20/EC	Future revision of the Directive 2001/20/EC to allow periodic submission of SUSARs to ECs with a covering brief /succinct assessment by the sponsor as per the current ENTR/CT3

2. Specific EFPIA Comments (presented in order of importance to EFPIA)

Page and Section Number	Comment and Rationale	Proposed Change to Text
Page 7 Section 4.3.3 (45) Expectedness	We note the introduction of a new requirement which strongly advises the sponsor to obtain an expectedness assessment from the investigator for all serious suspected ADRs. We have significant concerns on this point for the following reasons : • 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. • There are also concerns about consistency among investigators, and the fact that none of the internationally accepted guidances (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 and capturing in E2B). EFPIA have no objection to 4.3.3 (44) with respect to the sponsor taking into consideration an investigators assessment of expectedness if provided, but strongly consider that the subsequent paragraph (45) be deleted	*4.3.3 Expectedness* ~~*45. In the absence of information on the expectedness by the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express and opinion on this aspect. The expectedness assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator`s expectedness assessment, both the opinion of the investigator and the sponsor should be provided with the report*~~

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Page 11 Section 4.7.3.2 (75)	This section introduces the option of either direct or indirect reporting to EVCTM, as determined by the Member States. In these circumstances : • it is inevitable that different Competent Authorities will oblige different options, in which case, for any multinational trial, sponsors would be submitting directly to EVCTM for some CAs 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 MS in which the CA obliges the route of reporting which is not the sponsor`s choice. • we cannot see how anything else other than direct reporting would work for third country SUSARs as, if many sponsors choose MSs which ensure indirect reporting, this would place an undue burden on the Competent Authority(ies) 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 EV by the sponsor, the ICSR could then be duplicated by another CA which chose indirect reporting, especially for third country reports EFPIA therefore recommend that only one route is available. Our preference is for direct reporting by the sponsor as this is consistent with the proposed new PV 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. We could also accept indirect reporting by all CAs for SUSARs arising within the EU but acknowledge that this would be an	**EFPIA Preferred Option** *Section 4.7.3.2 reporting Modalities and Use of the European database – direct ~~and indirect~~ reporting* *75. As regards the input of information regarding SUSARs into EVCTM, Member States may ~~provide for one of the following measures :~~* • ***Obliging*** *~~the~~ 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* • *~~Obliging the sponsor to report only to the national competent authority of the Member State where the SUSAR occurred who, in turn, enters this information into EVCTN(hereinafter referred to as indirect reporting)~~* • *~~Leaving it to the sponsor to choose direct or indirect reporting~~* **EFPIA Second Option** *Section 4.7.3.2 reporting Modalities and Use of the European database – direct and indirect reporting* *75. As regards the input of information regarding SUSARs into EVCTM, Member States may provide for one of the following measures :*

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	additional burden for the authorities.	• *Obliging 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.* ***Direct reporting will be mandatory for reportable SUSARS from third countries*** • *Obliging the sponsor to report only to the national competent authority of the Member State where the SUSAR occurred who, in turn, enters this information into EVCTN(hereinafter referred to as indirect reporting).****Indirect reporting will only be available for SUSARs arising from within the EU*** • *Leaving it to the sponsor to choose direct or indirect reporting* ***for SUSARs arising from within the EU.***
Pages 12&13 4.7.3.3 (79, 80&81)	These sections currently sit under the overall heading of " Transitional Reporting Procedures" but , under (2) Reporting to EVCTM, 79, 80 and 81 refer to direct and indirect reporting . This appears to conflict with 4.7.3 (73) which states that the transitional period only applies until EVCTM functionality allows direct and indirect reporting under 4.7.3.2. Therefore reference to direct and indirect reporting under the	

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	transitional reporting procedure section is confusing as we assume that as soon as EV functionality allows these options, then the transition arrangements cease. Further clarity would be much appreciated.	
Page 6 Section 4.2.1 (28) and Page 8 Section 4.5 (48)	These sections define what is **not** a SUSAR for the purposes of expedited reporting and then cross refer to section 4.2.1 which does not actually give guidance on how to report such non-SUSARs, as implied. The section where some guidance **is** provided is Section 4.11.3. (page 15) The various options provided, while certainly appropriate for a significant issue which may impact study subject safety, may not be appropriate for some individual SUSAR reports e.g. to a non-IMP. EFPIA also note the apparent omission of a current provision for a sponsor to report spontaneous SUSARs from third countries where they market the IMP which is still pre authorisation in the EU. It is unclear if this was an inadvertent oversight or if such cases would now be considered to be a non – SUSAR. In addition, SUSARs occurring in a EU clinical trial are unlikely to come to the knowledge of another sponsor undertaking trials with the same IMP through spontaneous reporting. EFPIA therefore recommend that: • Section 4.5 (48) is amended to cross refer to Section 4.11.3 and not 4.2.1 as the former section is more relevant • 4.11.3 (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. For example, it may be appropriate to send a copy of the non SUSAR report to the manufacturer of the non IMP. EFPIA	*4.5* ***Adverse reactions not to be reported*** *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 ~~spontaneous reports~~, 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,

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	recommend that this report be submitted to the authorities under the provisions of Volume 9A. In addition, some reports which do qualify as SUSARs may also lead to additional actions beyond expedited reporting as highlighted in this section. • Section 4.5 (48) should be amended to include 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; reference to spontaneous reports should be deleted from 48 (second bullet)	these events/observations may require other action during a clinical trial such as : • **Notification of individual serious and unexpected ADR reports which do not qualify as SUSARs e.g. from non IMPS should be forwarded to the original marketing authorisation holder who can then report under the post marketing guidelines.** • **N.B some reports which qualify as SUSARs may also lead to additional actions beyond expedited reporting such as a substantial amendment or early termination of the trial.** **(EFPIA Note :Additional point to those already listed)**
Page 7 Section 4.4 (46) Page 12 Section 4.7.3.3 (78)	This final point on this page 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 encapsulate the complexity of business development agreements and introduces the potential for duplicate reporting. EFPIA therefore recommends the following additional sentence: 'The safety data exchange agreement between the respective sponsors must ensure that one party takes responsibility notification of SUSARs`.	*4.4 SUSARs to be reported* *- sponsored by another sponsor who is part of the same mother company or who holds a development agreement with the sponsor.* ***The safety data exchange agreement between the respective sponsors must ensure that one party takes responsibility for notification of SUSARs*** The same amendment applies to the second point in 4.7.3.3 (78)

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Page 14 4.11.1 (94)	There appears to be an error in the last part of the last sentence as it seems as if they are allowing routine unblinding of investigators which is in direct conflict with point 93 which stipulates that the investigator should only unblind an IMP if relevant to the safety of the clinical trial participant. On a routine basis , EFPIA consider that investigators need to have blind maintained as a general rule unless directly pertinent to the safety of their study participants We therefore recommend that " investigators" are removed from the list of persons for whom the access of unblinded information is routinely available	4.11.1 Blinded IMPs 94. Unblinded information should only be **routinely** accessible to those who need to be involved in the safety reporting to EVCTM, national Competent Authorities, ~~investigators~~, 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 their clinical trial participants.**
Page 12 Section 4.7.3.2 (76)	EFPIA fully appreciates that some sponsors may not have the resources or experience for direct reporting so provision in the guidance is needed to address this situation. Nevertheless, we are concerned that, despite the fact that final accountability will always reside with the sponsor, commercial partners which assume SUSAR reporting from academic collaborators could become exposed from a compliance perspective. In an investigator initiated trial situation, whereby a commercial partner may provide some funding, it is inevitable that many academic centres will wish to take this option. EFPIA therefore recommends that this option is modified to contain the caveat that delegation can occur if offered by the commercial partner, documented in the letter of agreement between the sponsor and commercial partner and on the understanding that compliance with reporting requirements remains with the sponsor.	*76 (second bullet point)* • *Where a commercial partner is involved (e.g. the marketing authorization holder of the IMP), delegate the direct submission to the partner,* ***if offered by the commercial partner and fully documented in any letter of agreement. Accountability for reporting compliance remains with the sponsor, even if the responsibility for SUSAR reporting to EVCTM is delegated.***

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Page 2 Section 1.2 (4)	This sentence may lead to confusion and is much less clear than the scope defined in the existing ENTR/CT 3 document. EFPIA recommends that the original wording be reinstated.	*This detailed guidance sets out guidance on the collection, verification and presentation and decoding procedures of adverse event/reaction reports arising from clinical trials on medicinal products for human use. In addition, it sets out the responsibilities of the concerned parties.* *This guidance applies to all clinical trials on medicinal products for human use within the scope of Directive 2001/20/EC conducted within the European Community (with at least one investigator site in the community). It applies to all investigational medicinal products for human use independently from their marketing authorisation status in any Member State whether or not investigational medicinal products are used under the conditions of the marketing authorisation.*
Page 7 Section 4.3.2 (40)	EFPIA considers that the need for investigator assessment of causality should be emphasised.	The assessment of causality ~~is often made~~ **should be undertaken** by the investigator