# 1. General SERVIER Comments

| General Comment | Proposed Amendment |
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| SERVIER 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:<br>• Introduction of the need for all national requirements to be consistent with procedures and timescales in Directive 2001/20/EC<br>• Clarification of the interface with safety reporting of authorised medicines under PV rules | |
| In streamlining the guidelines, however, we 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).<br>This results in a document which is :<br>• 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)<br>• less useful than the previous guideline in some sections which have been significantly shortened e.g. unblinding procedure is now omitted<br>• 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) | The sections to which these recommendations apply are as follows :<br>• 1.2 (5) – Scope of the guidance<br>• 1.3 - Definitions – Move to an Annex<br>• 2.2 – Definitions – Move to an Annex<br>• 2.2.2 (17) – quote full examples from ICH E2A<br>• 3 (23) Regarding the definition of adverse event, reference is made to ~~section 2.2.1~~ Annex xxx<br>• 4.2 Definitions – Move to an Annex<br>• 4.2.3 (34) – include reference from CT -1<br>• 4.3.2 (39 and 40) – include full ICH E2A reference |

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| SERVIER 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. | • 4.7.3.3 (77) Transitional Reporting procedures – give the full details of the SUSARs from section 4.4 (first and second bullet points)<br>• 4.11.1 Blinded IMPs – reinstate the unblinding procedure from the current detailed guidance |

## 2. Specific SERVIER Comments (presented in order of sections)

| Page and Section Number | Comment and Rationale | Proposed Change to Text |
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| p.4<br><br>Section 2.2 (12) (14) (15) and (16) (17) | Repetition between definition of « Serious adverse event » presented in section 2.2 (12) et "Serious event" presented in section 2.2.2 (14)<br><br>Same remark between sections 2.2.2 (16) and (17) | Definition 2.2 (12) - Move to an annex<br><br>~~2.2.2 Serious event (14)~~<br><br>~~An adverse event is 'serious' if it has the following characteristics/consequences :~~<br><br>~~– it results in death~~<br><br>~~– it is life-threatening~~<br><br>~~– it requires hospitalisation or prolongation of existing hospitalisation~~<br><br>~~– it results in persistent or significant disability or incapacity; or~~<br><br>~~– it is a congenital anomaly or birth effect~~<br><br>~~(15) These characteristics/consequences have to be considered at the time of the event~~ |
| p.4<br><br>Section 2.3.1 (19) | Precise if the period of time (48 hours) is expressed as working days or calendar days | Section 2.3.1 (19) "…The immediate report should be made within a very short time and under no circumstances exceed 48 hours (calendar days) following knowledge of the adverse event." |

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|---|---|---|
| p. 6<br>Section 4.2.1 (28)<br>and<br>Page 8<br>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 in 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. SERVIER 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. SERVIER therefore recommend that:<br>• 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<br>• 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.<br><br>Furthermore please precise in section 4.2.1 (28) the sentence *"which does not result from an interaction"*. It's not really obvious to know which product is concerned and please precise the modalities of reporting in this case. | *4.5* ***Adverse reactions not to be reported***<br><br>*48. It follows from section 4.4 that there is no need for the sponsor to report :*<br><br>• *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*<br><br>• *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*<br><br>***4.11.3 safety issues not falling within the definition of SUSAR – other ~~follow up~~ measures***<br><br>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 :<br><br>• **Notification of individual serious and unexpected ADR reports which do not qualify as SUSARs e.g. from non IMPS to the original marketing authorisation holder** |

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| p.7<br><br>Section 4.3.3 (43) and (45)<br><br>Expectedness | The reference document for evaluation of the "expectedness" is different between (34) reference Safety Information and (43) product information (e.g. IB or SmPC). Please precise which document let to evaluate the expectedness of a SADR.<br><br>The 'expectedness' should be assessed in the light of the reference safety information.<br>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 :<br>• 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."<br>• 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.<br>• Practical issues in training and retraining all investigators every time the reference safety information is updated.<br>• 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.<br>• 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 | *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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| | data field and capturing in E2B).<br>SERVIER 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 | |
| p.8<br>Section 4.4 (47) | It's more appropriate to compile all information relating to the transitional reporting procedures in the same section and please precise what are exactly the "additional SUSARs" = SUSARs as currently defined ? | Move the section 4.4 (47) into section 4.7.3.3 |
| p.8<br>Section 4.7 and section 4.8 | The title of this section is unclear and the term 'to national competent authority' is not appropriate due to mention of reporting to EVCTM (i.e. EMA) | 4.7 Modalities of reporting of fatal or life-threatening SUSARs<br>The same amendment applies to the title of the section 4.8 |
| p.11<br>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.<br>In these circumstances :<br>• 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.<br>• 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.<br>• 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 | **SERVIER Preferred Option**<br>*Section 4.7.3.2 reporting Modalities and Use of the European database – direct ~~and indirect~~ reporting*<br>*75. As regards the input of information regarding SUSARs into EVCTM, Member States may ~~provide for one of the following measures :~~*<br>• ***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*<br>• *~~Obliging the sponsor to report only to the national competent authority of the Member State where~~* |

| Page and Section Number | Comment and Rationale | Proposed Change to Text |
|---|---|---|
| | undue burden on the Competent Authority(ies) concerned.<br>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<br>SERVIER 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 additional burden for the authorities. | *the SUSAR occurred who, in turn, enters this information into EVCTM (hereinafter referred to as indirect reporting)*<br>• ~~*Leaving it to the sponsor to choose direct or indirect reporting*~~<br>**SERVIER Second Option**<br>*Section 4.7.3.2 reporting Modalities and Use of the European database – direct and indirect reporting*<br>*75. As regards the input of information regarding SUSARs into EVCTM, Member States may provide for one of the following measures :*<br>• *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***<br>• *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***<br>• *Leaving it to the sponsor to choose direct or* |

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| | | *indirect reporting* ***for SUSARs arising from within the EU.*** |
| p. 12&13<br><br>Section 4.7.3.3<br><br>(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 transitional reporting procedure section is confusing as we assume that as soon as EV functionality allows these options, then the transition arrangements cease.<br>Further clarity would be much appreciated.<br><br>Furthermore, it will be more comprehensive if the sponsor's responsibilities and MS's responsibilities are separated. | |

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| p. 14<br>Section 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 unbinding 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 , SERVIER consider that investigators need to have blind maintained as a general rule unless directly pertinent to the safety of their study participants<br>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<br>94. Unblinded information should only be **routinely** accessible to those who need to e involved in the safety reporting to EVCTM, national Competent Authorities, i~~nvestigators~~, 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.** |
| p.15<br>Section 4.11.1 (97) | Please precise if the paragraph 97 concerns the disease related events occurring in morbi-mortality trials and potentially not subject to systematic unblinding and expedited reporting (see section 95) or not. | |
| p. 16<br>Section 5 (104) | Following ICH E2F the DSUR should be submitted to national competent authority. The synopsis only is provided to Ethics Committee . | 104. The addressee of the complete report is the national competent authority of the member state concerned. The addressee of the synopsis is the Ethics committee of the member state concerned. |