Public consultation document – draft revised version of 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

Norgine welcomes the opportunity to comment on this European Commission Consultation. In particular, the incorporation of previous guidance documents into a single simplified guidance is welcome.

As a general comment, changes that will be made once the EVCTM functionalities are enhanced, (paragraphs 107, 109) or transitional reporting procedures (Section 4.7.3.3) can be communicated in a separate document e.g. as implementation plan once this guidance becomes effective, rather than including them in this document.

2. SPECIFIC COMMENTS ON TEXT

Section	Paragraph No.	Comment, Rationale and Proposed Changes
1.2: Scope	Paragraph 4	The scope of this detailed guidance is the scope of Directive 2001/20/EC, i.e. clinical trials as defined in Directive 2001/20/EC and performed in at least one Member State of the Union. **Suggest rewording** The scope of this detailed guidance is the scope of Directive 2001/20/EC, i.e. clinical trials as defined in Directive 2001/20/EC and ~~performed~~ **authorised** in at least one Member State of the Union.

1.3: Definitions	Paragraph 6	The definitions contained in Directive 2001/20/EC, its implementing acts and relevant guidance documents in the current version also apply in respect of this guidance. **Comment** **Please clarify what 'its implementing acts' refers to. Is it implementing acts at the level of Member States?**
2.2.2: 'Serious event'	Paragraph 14	**Comment** Could add: • *Other medically important condition* And then give the definition in paragraph 16
2.2.2: 'Serious event'	Paragraph 16	Medical events may jeopardise the clinical trial participant …….. **Suggest rewording** **Some m**edical events may jeopardise the clinical trial participant……..
2.3.1: Immediate reporting and follow up report	Paragraph 19	…….under no circumstance exceed 48 hours…… **Comment** ……under no circumstance exceed **24** hours……**would be more suitable especially with 7 calendar day SUSARs**
2.3.1: Immediate reporting and follow up report	Paragraph 20	The follow-up report should allow the sponsor to assess in detail …… **Comment** **What is the timeline for follow-up report following immediate report?**
2.3.2: Non-immediate reporting	-------	……the investigator shall report within the appropriate timeframe taking account of the specificities of the trial and of the serious adverse event, as well as possible guidance in the IB. **Comment** **The reporting timeframe is open to interpretation and introduce inconsistencies in investigator reporting. More specific guidance would be helpful.**

3: Reporting non-serious	Paragraph 22	*'Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.*' **Comment** **Please clarify – *'according to the reporting requirements'*. Is this referring to Member State reporting requirements? What are the requirements for reporting non-serious AEs? Is there any guidance for 'time periods' that can be specified in the protocol?**
4.2.4: SUSARs occurring after the end of the trial	Paragraph 35	The definition of SUSAR is independent of whether the clinical trial has ended ('post-study SUSAR') or is still ongoing. The obligations related to SUSAR reporting do not finish with the end of the trial. **Comment** **Please clarify. Does it mean post study SUSARs should be reported indefinitely? Will the reports be regarded as originating from a study or will they be spontaneous reports.**
4..:. 'Seriousness'	Paragraph 36	The sponsor is responsible for ensuring that the reported reaction is serious. **Suggest rewording** The sponsor is responsible for ensuring that **only serious** ~~the reported~~ reaction is **reported** ~~serious~~.
4.3.3: Expectedness	Paragraph 44 & Paragraph 45	If information on the expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor. **Comment** **Since the product information used by the sponsor and the investigator is the same, is it anticipated that the assessment can differ between the sponsor and the investigator? Is the investigator legally required to provide assessment of expectedness? We would propose that the expectedness is assessed by the sponsor as they have a fuller picture of the pattern of all events.**
4.5: *Adverse reactions*	Paragraph 48	SUSARs occurring in a clinical trial performed (partly or exclusively) in the EU for which he is not the sponsor. These SUSARs may come to the knowledge of the sponsor through spontaneous reports,

not to be reported		publications (such as academic literature), or regulatory authorities. **<u>Comment</u>** **Since these SUSARs may come through spontaneous reports, and if the organisation is the MAH for the IMP, is there no obligation to report as MAH?**
4.7.1.2: Content of initial reporting	Paragraph 60	Relevant information includes, at least, the following information: - Valid EudraCT number: **Comment** **Is relevant information to be interpreted as the minimum information for a report to be expedited? What about SUSARs originating outside the EEA which may not have a EudraCT number?**
4.10: *Informing the investigator*	Paragraph 91	If appropriate, the information on SUSARs should be aggregated in a line listing of SUSARs …… This line listing should be accompanied by a concise summary of the evolving safety profile of the IMP. **<u>Comment</u>** **This paragraph does not carry with it a sense of urgency in notifying investigators. If notification is in the form of aggregated line listing, there is no need for 'immediate' notification to the investigator. It seems notification is driven by volume of SUSARs generated, rather than the significance of the safety concern.** **Please add the purpose of the obligation to notify investigators, in line with paragraphs 11 and 25.**
4.11.1: Blinded IMPs	Paragraph 97	For cases where the SUSAR becomes apparent only after the trial has ended, reference is made to section 4.2.4. **<u>Comment</u>** **This paragraph does not relate to post-study SUSAR which is spontaneously reported by investigator. It appears to relate to a SUSAR identified where the blind was maintained until the**

		end of the trial. Guidance is therefore required for reporting of SUSARs where the unblinding takes place at the conclusion of the study.