SUBMISSION OF COMMENTS ON DRAFT EC 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 NOVARTIS PHARMACEUTICALS.

GENERAL COMMENTS

Novartis supports efforts to improve and clarify the detailed rules for safety reporting in clinical trials, and to consolidate three existing guidances into one. However, we feel the proposed draft does not effectively meet that objective. It has taken three useful, detailed guidances and merged them into a single guideline that is less specific and informative than the originals. A significant amount of instruction that is valuable to industry appears to have been deleted from the proposal, conceivably exposing elements of the ADR process to broader interpretation by sponsors, making it more difficult to ensure that the thinking of sponsors' is in synch with that of regulators.

We recommend including all original content from the three existing guidances in the proposed replacement guidance, except for material has become obsolete or has been superseded with revised text.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
1.2 Scope item #4	Although Directive 2001/20/EC is cited as a source of additional details on scope of trials, it might be useful to repeat that the proposed guidance pertains to interventional trials (e.g. Directive Article 1)	Consider including the Directive's scope (instead of simply cross-referencing it).
2.2 Serious	The draft Guidance includes "medically significant" events as a seriousness criterion, but the cross-referenced Directive	Consider using the complete ICH definition in the Directive.

AE	does not.	
2.2.2 item #17	ICH E2A is cross-referenced for examples of "medically significant" events. This means the user needs to consult three documents at one time for the required information: The draft Guidance, the Directive, and the ICH publication.	Consider including the ICH text as an appendix to the Guidance.
2.3.1 Timelines	The definition of "immediate" for the purpose of investigator SAE reporting to sponsors is a new one (i.e. 48 hours). This should also be codified in the Directive.	Consider adding the new requirement to the Directive.
4.2 Suspected ADR item #27	The definition of suspected ADR presented in the draft Guidance is not fully consistent with the ICH definition, particularly with respect to causation.	Consider using the ICH E2A language with respect to causal attribution.
4.2.3 Causality	Only investigator causality is mentioned in this section, but the existing guidance on serious adverse events (ENTR/CRT3 sections 4.2.2 and 4.2.5) and the Directive also refer to sponsor assessment. The intent of this section is not clear. Is the sponsor still expected to assess all SAEs? If not, how can a sponsor, as stated in item #41, disagree with an investigator? In item #39, the concept of a "reasonable causal relationship" appears, but it was not originally mentioned in the definition of "adverse reaction". In items #39 and #40, ICH E2A is cited with reference to attribution terms, scales, and the role of the investigator. We were unable to determine the specific sections of the ICH documents being cited and would like to see clearer reference made to the actual language.	Please clarify these points, as they are currently ambiguous in the proposed Guidance.
4.3.3 Expectedness Item #45	The introduction of investigator "expectedness" assessments is a new and unanticipated concept. Investigators are trained to forward all SAEs to the sponsor, regardless of expectedness. Expectedness assessment is a complex and subjective discipline that requires detailed training, rigid adherence to each sponsor's operating	Propose leaving expectedness assessment to the sponsor, who is experienced in such work and can standardize it across development projects.

	procedures, and continuing oversight by sponsors. Involving investigators in listedness assessment has a regulatory dimension to the case report workflow and adds no value to the SAE process. In fact, it is likely to create a massive additional workload for investigators and sponsors and lead to inconsistencies within studies, sites, indications and products.	
4.7.1.2 Initial reporting Item #60 and #69	(#60) It could be useful to add other factors that would constitute relevant information requiring follow-up e.g. changes in: outcome, coded events (PT level), reporter causality, etc. (#69) The term "lack of causality" is subject to interpretation.	Consider adding additional examples. Consider rewording to indicate that this refers to no causal relationship suspected (rather than unreported causality).
4.7.11.2 Comparator SUSARs	The existing guidance on serious adverse events (ENTR/CRT3 section 5.1.4) recommends transmitting comparator SUSARs to the appropriate MAH. The draft Guidance omits this language.	Please clarify if the intent is that sponsors do not need to share comparator SUSARs with other sponsors.
6.2 EVCTM Items #108 and #109	(#108) Further details on quantitative statistical methods would be useful to sponsors. Can we assume that the Guideline on signal detection methods in Eudravigilance is the reference document here (EMEA/106464/2006)? (#109) Further details on the criteria for SUSAR Alerts relevant to Member States would be useful to sponsors.	Please clarify the appropriate reference document for signal detection. We recommend publishing alert criteria if these are to be standard across all trials, or communicating them to the sponsor if they are trial-specific.