August 2010

European Commission
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Response to 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')

In an area where global pharmacovigilance for multinational clinical trials is a complex network of regulatory agencies and licensing partners we greatly support the Commission's efforts to achieve a greater harmonization of adverse event management and reporting across regions. Besides harmonization, the focus should remain on data quality improvement since failure to effectively manage safety data can affect the well-being of patients, jeopardize the reputation of a company and impact key relationships with competent authorities (CA).

Our comments to the 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') are listed below:

- Regarding the definition of a serious event, it would increase clarity to elaborate on the criterion 'hospitalization' with regards to hospitalizations that were planned before the patient started the trial and hospitalizations that are arranged for convenience.
- Although a pregnancy that is reported in a clinical trial is not considered a serious adverse event, we consider it beneficial to include some guidance on the processing of pregnancy reports, including pregnancies in partners of patients participating in a clinical trial to ensure the safety of these individuals.
- Currently a number of guidelines specifying various aspects of clinical trials have been published. It is great to see that efforts are made to replace multiple guidance/Q&A documents by one joint document. This should be extended further to reduce the number of duplications and increase consistency.
  Despite the existence of the 'Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in clinical trials' document we have the experience that the understanding of the IMP/NIMP definition is still inconsistent. Moreover, following different wording might result in variable interpretations and should consider revision: this draft ENTR/CT 3 guideline clearly states that any reaction to a NIMP which doesn't result from an interaction with an IMP is not a SUSAR, while the 'Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in clinical trials' reports that these type of reactions should be reported by the sponsor as a SUSAR in accordance with Article 17 of the Directive 2001/20/EC where 1.(a) and (b) state that all SUSARs require expedited reporting without specification of IMP/NIMP drug type.
  In addition, this 'Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in clinical trials' document only reports IMP and NIMP drug types while it seems that not all medicinal products taken during a clinical trial fall into one of both categories as specified in ID 014 of the 'Questions & Answers specific to adverse reaction reporting in clinical trials version 1.0' document. Since this Q&A document will be replaced by this revised

ENTR/CT 3 document, an overview of all possible drug types, including their definitions and corresponding reporting guidelines would provide more clarity.

- Also item ID007, addressed in above mentioned Q&A document, is not implemented in this revised guideline although we do consider this item to contain valuable practical aspects for the calculation of the reporting timeline in case an event becomes fatal or life-threatening during follow up before submission of the initial report.
- The degree of causality between an investigational medicinal product and an adverse event is currently described using multiple possible terms. Harmonization of the causality assessment using a standard international nomenclature would facilitate the assessment, reduce misinterpretations that might result in over-reporting or, more worse, under-reporting and avoid discrepancy tables to align different assessments with the limited options of the safety database.
- With regard to the expectedness assessment following inconsistency is noted and might require rephrasing: item 34 states that the unexpectedness of an adverse reaction is determined by the sponsor according to the reference safety information, while item 45 reports that the sponsor should consult the reporting investigator to encourage him to express an opinion on this aspect.
- Eudravigilance has become indispensable in global pharmacovigilance. As a user, the harmonization of national reporting requirements and the availability of a joint reporting tool has significantly facilitated expedited reporting. It is a pity however that despite such a huge effort in installing this system, companies still need to consult each Member State individually regarding their preference in direct or indirect reporting. It might be worthwhile to align this in the future as well. Furthermore it is disappointing and inefficient that third countries don't accept the European format for SUSAR reports preventing the harmonization to a more global level.
- The part on reporting of SUSARs to the Ethics Committees (ECs) is reduced. The recommendation to report only SUSARs that have occurred in the corresponding Member State together with 6 monthly line listings in the current version is replaced by cross-references to the guidelines on reporting to the CAs, suggesting individual case reporting to ECs of all SUSARs regardless of country of origin and abolishment of 6 monthly line listings. Currently the management of expedited reporting to Ethics Committees for multinational trials is burdensome and harmonization would be embraced.

Yours sincerely,

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