Final Concept Paper
E3 Q&As
E3: Structure and Content of Clinical Study Reports

Dated and endorsed by the Steering Committee on 15 June 2011

Type of Harmonization Actions Proposed

- Preparation of a Question and Answers (Q&A) document for International Conference on Harmonisation (ICH) Guideline E3, *Structure and Content of Clinical Study Reports,* for the following purposes:
  - Alignment of E3 with the requirements of the Common Technical Document (CTD), particularly the requirements for electronic submission of this document (the "eCTD").
  - Clarification of other issues encountered since the implementation of E3 (1996) that hinder consistent implementation of that Guideline.
- Establishment of an ICH Implementation Working Group (IWG) to draft a Q&A document to E3.

Statement of the Perceived Problem

- Guidelines issued by US regulatory bodies are not requirements, and flexibility is inherent in their use. Nonetheless, there is considerable confusion across the industry about whether E3 is a Guideline or is actually intended as a required template.
  - The M4 Guidelines associated with the CTD refer to specific structural elements described in E3 (e.g., Clinical Study Report [CSR] section headings), leading many companies to interpret E3 as a template (i.e., a requirement).
  - However, use of E3 as a template without thoughtful interpretation may result in missing, redundant, and suboptimal presentation of information within CSRs. The problem may be exacerbated when E3 is used for studies for which it was not designed (e.g., exploratory studies, pharmacokinetic studies, and studies with combination products).
- These issues can lead to less than optimal presentations, resulting in potential delays for both the sponsor and regulatory reviewer.

Issues to be Resolved

- Content and Structure Issues of E3
  - Clarification of whether E3 is a guideline or template: Some sponsors create CSRs that do not deviate from any of the structure and content specified in E3, maintaining the E3 Table of Contents (TOC) and all elements stipulated in E3. Other sponsors interpret E3 more broadly, modifying the TOC and at the same time adding, deleting, and/or rearranging content.
  - Guidance clarifying that E3 is not intended to be followed rigidly if modifications of that Guideline can lead to better display and communication of information. It should be made clear that variations of E3 that maintain the goal of harmonized reporting of conduct and results of clinical trials are acceptable, as long as important deviations from E3 are explained.
  - Guidance on how to report studies that fall outside the original scope of E3: The current E3 TOC does not include certain information, such as results of pharmacokinetic, pharmacodynamic, quality of life, and other investigations.

- Appendices Issues
  - Required appendices in E3 include many documents now available in the Trial Master File (TMF; in accordance with E6) or data otherwise included in a CTD-based regulatory submission (in accordance with M4). It should be made clear that E3 allows references to documents in other locations.
  - Some regulatory authorities[1] have already reduced the number of appendices stipulated in E3. However, other regulatory authorities require submission of all appendices, even if the appendix is not relevant to the application. The Q&A should discourage such requirements.
  - Re-evaluation of appendices in E3 to allow the following:
    - Elimination of redundant appendices (because the information regularly appears in the TMF).
    - Identification of appendices necessary to reviewers during review of a CSR.
    - Making it clear that it is acceptable and indeed encouraged to include new appendices appropriate to the study and that sponsors should add new appendices to accommodate the increasing requirements for documentation and/or new types of studies (e.g., biomarkers, device details, etc).

      Note that the Study Tagging Files (STFs) required for an electronic submission of a CTD would need to reflect any changes made to the appendices in E3.
- Terminology Issues
  - Because E3 was an early ICH Guideline, some of the terms and concepts in E3 are discrepant from those found in other initiatives or guidelines.[2]
  - Lack of standardized terminology undermines the goal of harmonization; standardized terminology would aid this effort. Terminology in question includes, but is not limited to the following, all of which are used in E3: *other serious adverse events, study initiation date, protocol violations vs. deviations.*

Background to the Proposal

Since the implementation of the CTD in 2001, a group of experienced medical writers affiliated with the Medical Writing Special Interest Area Community (MW SIAC) of the Drug Information Association (DIA) have expressed concern that E3, one of the earliest ICH Guidelines (1996), was not aligned with the CTD and the two give conflicting advice. This situation became particularly apparent when electronic submission of the CTD was implemented.

In 2005, at a special presentation at an FDA ICH public meeting, the MW SIAC alerted ICH to the issues described above. In 2009, the DIA MW SIAC formed the ICH E3 Task Force to further address these concerns.

Between 2010 and early 2011, this Task Force described these concerns to FDA members familiar with both the E3 Guideline and CTD submissions. Upon review of the issues, FDA members expressed support for a Q&A to E3 that would align it with the CTD, particularly the requirements for eCTD format, and clarify other aspects of E3, emphasizing what might seem apparent - that ICH Guidelines are not rigid, but can be modified to enhance communication, generally with explanations of the modifications.

Composition of the Implementation Working Group

The IWG will consist of members nominated by the six sponsors of the ICH, as well as Health Canada, WHO, EFTA, and other Interested Parties, as appropriate. Members of the IWG will be familiar with the

[1] EMA in Note for Guidance on the Inclusion of Appendices to Clinical Study Reports in Marketing Authorisation Applications (CHMP/EWP/2998/03).

[2] Protocol Representation Model (CDISC/HL7); ICH E2D (*Step 4*), Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting, 2003.

current E3 Guideline and experienced in the preparation and review of both CSRs and submissions in eCTD format.

Timing

- **April 2011:** Submission of Concept paper to ICH Steering Committee in advance of the Steering Committee's teleconference (anticipated in April).
- **June 2011:** Presentation of revised Concept Paper at ICH meeting in Cincinnati, Ohio, 11 to 16 June 2011.
- **June 2012:** Finalization of Q&A document via teleconference and postal signoff.