

Alan Goldhammer, PhD
Associate Vice President,
US Regulatory Affairs



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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 01D-0435; Draft Guidance on ICH Electronic Common Technical Document Specification; 67 Federal Register 40948

Dear Sir/Madam:

The following comments on the above noted draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2001, our members invested over \$30 billion in the discovery and development of new medicines.

PhRMA offers the FDA both general and specific comments on this draft guidance.

General Comments

- The specification should allow the option of 5 levels of headings (as opposed to 4). Four levels will not provide enough levels to represent the necessary sections and subsections in certain documents.
- PhRMA believes that granularity is too fine. For example, the specification proposes that in the Drug Substance General information section there should be separate PDFs for Nomenclature, Structure, Properties, etc. In PhRMA's opinion this will create too many small PDFs, in the case where all PDFs address the physico-chemical characteristics of the drug substance. PhRMA proposes that the author be given the option of combining specifications into a single PDF or creating separate PDFs.
- A recurring concern is that the eCTD specification differs slightly from the CTD specification in certain areas, and that more attention needs to be paid towards consistency between the eCTD and the CTD.

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Specific Comments

ICH eCTD Specification

The **Process** Section says "Since the issuance of guidelines is the responsibility of the regulatory authorities, in line with the standards ICH process..."

Change standards to standard.

The **eCTD Template** Section says, "The ICH web site includes an eCTD Template that is an empty directory structure..."

This empty template could not be found on the ICH web site. Instead, a file and folder model eCTD containing placeholder PDF documents was found.

Appendix 3 General Considerations for the CTD Modules

In **Table 3-3** the folder name for the Quality Overall Summary is "quality- overall-summary."

There is a space before "overall" and this violates the naming conventions established for files and folders.

For **Table 3-4** to match the **Notice to Applicants, Volume 2B, incorporating the Common Technical Document (CTD) (May 2002)** the following changes are needed

- Section 3.2.S.4.2 should be changed to 3.2.S.4.3.
- Section 3.2.S.4.1 should be changed to 3.2.S.4.2.
- A new entry needs to be added between 3.2.P Product 1 and 3.2.P.3 Manufacturer as follows:

3.2.P.2	Pharmaceutical Development	pharmaceutical-development
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- Section 3.2.P.5.1 should be changed to 3.2.P.5.2.
- Section 3.2.P.5.2 should be changed to 3.2.P.5.3
- Section 3.2.A.3 the description and folder name should be excipients instead of excipient as in the CTD.

3.2.A3	Novel Excipient 1 ⁴	novel-excipient-name-1
3.2.A3	Novel Excipients 1 ⁴	novel-excipients-name-1

In **Figure 3-2**, the "references" folder should be removed.

In **Table 3-5** the column heading is repeated.

In **Table 3-5** Section 4.2.1.1 the folder name "Primary-pharmacodynamics" violates the naming conventions. It should be "primary-pharmacodynamics."

In **Table 3-5** Section 4.2.3.4.2 under the Description column, the phrase "...be appropriately include..." should be changed to "...be appropriately included..."

Just before **Figure 3-3** there is a page break that should be removed.

In **Table 3-6**, the entry before Section 5.4, the Description and folder name should be changed.

	"Study n"	study-n
	"Study 3"	study-3

In **Figure 3-4** the folder "nonclinical-overview" should be removed.

In the e-CTD **DTD specification**, the organization of the case report forms (CRFs) and individual patient listings (datasets) (Element **m5-3-7-case-report-forms-and-individual-patient-listings**) does not follow the standards put in place with FDA's electronic submission guidances (Guidance for Industry: Providing Regulatory Submissions in Electronic Format — NDAs, January 1999, and Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications, November 1999, REVISED). While the DTD does allow for organization of CRFs by study, there is no provision for further organization by study site. Likewise, it appears that the DTD specifies that datasets for each study be placed in the same folders as the patient CRFs. Further, there is no provision for dataset documentation (annotated CRF and data definition document) in the DTD. PhRMA proposes that for each study:

- a) CRFs and individual patient listings are organized in separate folders;
- b) either the CRFs is further organized by study site folders, or the CRF naming convention is changed from only the patient number to a combination site-patient number; and
- c) individual patient listings (datasets) are accompanied by appropriate documentation (annotated CRF and data definition document).

Appendix 5 Region Specific Information Including Transmission and Receipt

In Table 5-3, the EU will require DVD media for submissions above 650 MB. Many EU submissions currently require two CD-ROMs, but according to this table FDA will NOT accept a CD unless everything will fit on one CD-ROM. Since there are different formats for DVD (e.g. DVD-RAM, DVD-ROM, DVD+RW, ASMO format, MMVF format, etc), FDA should be more specific on exactly what DVD formats are needed and make sure all member states can accommodate the format?

Appendix 6 The eCTD XML Submission

In **Table 6-8** it is not clear what attributes are optional (e.g. ID) and which attributes are required. It would be helpful to include an optional/mandatory status in this table.

In **Table 6-8** the meaning of "Font-library" is not clear.

Appendix 7 Specification for Submission Formats

On page 7-1 the last paragraph says "Agencies cannot guarantee the availability of any fonts except Times New Roman, Arial and Courier and fonts supported in the Acrobat product set itself. Therefore, all additional fonts used in the PDF files should be embedded to ensure that those fonts would always be available to the reviewer." However, Adobe has not always supported these fonts. For example, they dropped Arial in Acrobat 4.0 and replaced it with Helvetica. This has caused some sponsors problems and some reports didn't print correctly when font substitution was done. It sounds like the Agencies will make sure they continue to have support for Times New Roman, Arial and Courier. If this is not true, it would be safest to always embed fonts.

PhRMA trusts that these comments are useful to the Agency as it moves towards finalizing this ICH Guidance.

Sincerely,

