Alan Goldhammer, PhD
Associate Vice President,
US Regulatory Affairs

PhRMA

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December 17, 2003

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

Re: Docket Number 2003D-0465; Providing Regulatory Submissions in Electronic Format - General Considerations; Draft Guidance; 68 Federal Register 60395

Dear Sir/Madam:

The following comments on the above draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA).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 2002, our members invested over $32 billion in the discovery and development of new medicines.

PhRMA supports the Food and Drug Administration's (FDA) desire to utilize common technologies for electronic submissions that are consistent across the centers of FDA.

General and Specific Comments:

PhRMA believes this guidance document should be aligned with the other electronic submission guidance documents issued in August 2003 and the ICH eCTD Specification. This draft guidance refers to only the NDA, BLA and IND. Although in the draft FDA electronic submission guidance (issued August 2003) FDA recommends sponsors file submissions in the eCTD format, there is no mention of CTD/eCTD and the use of the XML backbone structure in this guidance. Because sponsors and FDA interact electronically in accordance with many electronic formats and standards—e.g., eNDA, eCTD, eBLA, and hybrids of these and others—it is important for this ***General Considerations*** guidance to address all of these standards. However, the application of this guidance to the submission of advertising and promotional materials via electronic means is problematic and we strongly encourage the Agency to consider developing a Draft Guidance that is specific to the submission of advertising and promotional materials.

The 1999 section on "Electronic Signatures" does not appear in the 2003 version. This *implies* that the FDA is now willing to accept electronic signatures. The August NDA Annual Reports draft Guidance said electronic signatures were not endorsed. Clarification would be appreciated.

A subsection should be added to section IV that describes file size standards, especially because the current 50MB limitation may no longer be relevant since ICH has raised the limit at 100MB. Alternatively, it could be covered in section IV, subsection F.

2003D-0465 C 1

Pharmaceutical Research and Manufacturers of America

1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3533• FAX: 202-835-3597 • E-Mail: agoldham@phrma org

It would be helpful if relevant, related guidance documents were referenced from this guidance.

Page 2, Footnote 3
The footnote mentions Part 11, Electronic Records; Electronic Signatures – Scope and Application, which was issued in September 2003. The document on the FDA website is dated August 2003. Is this the same document?

IV. WHAT FILE FORMATS SHOULD I USE FOR ELECTRONIC DOCUMENTS?
In lines 88-89, is the FDA going to specify the heading levels associated with a "well-structured" table of contents (e.g., Level 1-4)?

In lines 91-92, the term common software formats is too vague; expected formats should be identified.

In line 99, a reference to ICH should be added.

IV. A. Version
In line 105 it says "Acrobat Reader version 4.0, and above..." This should be stated as "the Acrobat Reader version currently available from Adobe and below", since the sponsors will not be able to make the files forward compatible.

In line 106 it says "... with the search plug in." We recommend deleting this for the eCTD since ICH has recommended Acrobat Catalog not be used in regulatory submissions.

IV. B. Fonts
In line 124, the word "one" should be replaced with "those" and the sentence edited. We also recommend Table 1 be removed. The ICH eCTD Specification recommends "*Using only True Type or Adobe Type 1 fonts*" and this document should be compatible.

If Table 1 on line 128 is retained, (a) we suggest this table be reviewed and harmonized at ICH; and (b) it would be valuable to add a separate column that differentiates the font as described in a word processor from the PDF font as described when embedded, e.g., authoring font TimesNewRoman; embedded font TimeNewRomPSMT.

Line 131 should be reconciled with recent ICH Specification for the eCTD.

Line 139 should be reconciled with recent ICH Specification for the eCTD.

In Lines 141-142, we recommend this guidance explicitly state that no background shadowing be used.

IV. D. Page Size and Margins
In lines 156-162 it specifies the sizes of the margins and the location of headers/footers. The ¾ of an inch recommendation may be too restrictive for sponsors preparing content that will be delivered to more than one agency. We recommend that FDA adopt the margins as specified in the eCTD Specification:

> A sufficient margin (at least 2.5 cm) on the left side of each page should be provided to avoid obscuring information if the reviewer subsequently prints and binds the pages for temporary use. For pages in landscape orientation (typically tables and publications), smaller margins (at least 2.0 cm at the top and 0.8 cm left and right) allow more information to be displayed legibly, on the page (see Fonts). Header and footer information can appear within these margins but not so close to the page edge to risk being lost upon printing.

IV. E. Source of Electronic Document
In lines 169-170, if scanned legacy documents are to undergo a 100% quality check following optical character recognition, there will be a substantial impact on sponsor resources that is both time-consuming and very expensive.

IV. F. Methods for Creating PDF Documents and Images
In lines 207-208, the guidance should instruct people to contact the FDA if submissions containing medical images are planned. Otherwise, there is a risk that people may think it is acceptable to simply collect the images and send them to the FDA. Will the FDA make a separate guidance available in the future for medical image submissions?

Lines 228-235 should be reviewed at the ICH level. References to these standards would enhance compliance to the specifications.

IV. G. Hypertext Linking and Bookmarks
Lines 240-241 should be agreed at the ICH level.

Lines 246-248 need to apply to multiple submission types, e.g., eNDA and eCTD; therefore, it should be expanded and explicit for each, e.g., eCTD would include module links.

In lines 249-251, since the FDA is implementing the eCTD submission format, use of the XML backbone should be the initial choice followed by use of bookmarks for roadmap, main table of contents and item table of contents for the eNDA or eBLA format submissions.

In line 252, to enhance the ease of review, the sponsor may choose to include additional bookmark entries compared to that in a report table of contents (e.g., In a Clinical Study Report table of contents, there could be an entry just for the study protocol title, however, in the bookmark hierarchy all entries from the study protocol table of contents could be present). Will that still be acceptable with the FDA?

IV. H. Page Numbering
Line 278 refers to splitting a file "because its size (e.g., > 50 MB)". The ICH M2 Expert Working Group has raised the size that a document must reach before it is split to 100 MB.

IV. I. Document Information Fields
In lines 289-290, it would be valuable to identify that for eCTD submissions, this is a regional requirement, because it does not represent ICH requirements.

In lines 290-291, what are FDA's plans for updating the specific guidance documents?

IV. J. Open Dialog Box
In lines 296-297 it says, "If there are no bookmarks, we recommend that you set the initial view as *Page* only." This is contradictory to Page 7, Lines 248-252. There should always be some type of bookmark (e.g., Go to Main TOC)

IV. K. Naming PDF Files
In line 308 it says "... you can use file names up to 32 characters in length..." The eCTD Specification says "The maximum length of a path is 230 characters, including file name, and extension." We recommend these two documents be consistent.

In lines 309-311 it says, "We recommend that you avoid using punctuation, dashes, spaces, ...". However the ICH eCTD naming conventions and those published in the August 2003 draft FDA e-submission guidance use only lower case characters and no special characters may be included in file or folder names, other than hyphens (-). We feel this Guidance should be aligned with the eCTD Specification.

IV. M. Indexing PDF Documents
Lines 322-342 should be removed or should not apply to eCTD submissions because the ICH eCTD Specification recommends no full text indexes.

V. WHAT FILE FORMATS SHOULD I USE FOR ELECTRONIC DATASETS?
In lines 354-360, molfiles are not identified, but they are described later as a standard. An addition should be included here.

V A. 5. Content of Datasets and Organization
In lines 406 it says "...files should be organized so that their size is generally less than 50 MB per file." ICH has a maximum file size for a document, and it is 100 MB.

V. D. Molfiles
Line 474 contains an invalid link.

VI. B. 1. Where do I send the electronic submission?
In line 522 CBER recommends a minimum of two copies of the submission. PhRMA believes that one copy should be sufficient and is consistent with the CDER requirement.

In lines 540-543 we recommend that the address of CDER's Central Document Room be included.

Line 549 contains an invalid link.

VI. B. 2. What type of media should I use?
The table between lines 603-604 needs to be revised. "CD-ROM ISO 9660" should be changed to "CD-R Joliet Specification". DVD-RAM should be added as it was recently approved by ICH. The specification for NT server 4.0 with NT backup should be expanded to include, at a minimum, Win2000. If backup exec is referring to VERITAS BackupExec, it should be explicitly stated. It would also be beneficial if a version number were included.

In lines 631-632, if sufficient information is included on the CD-ROM itself, are sponsors still required to include information on the jewel case?

Appendix A: CBER Roadmap file
Lines 688-744 contain a description of the roadmap file. We recommend this section be removed since CBER plans to implement the eCTD and the eCTD does not require a roadmap file. What should be the procedure for eCTD format submissions where there is no roadmap file? Does the XML backbone need to be included on all media units?

Appendix A: CFSAN
In line 771-772 it says "...the second copy...", but this is in conflict with line 557.

Again, PhRMA appreciates the opportunity to comment on the details of the proposal, and applaud FDA's initiative to update the General Considerations document.

Sincerely,

Alan Goldhamer