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November 29, 2001

Docket Management Branch
FDA
HFA-305, Room 1061
5630 Fisher's Lane
Rockville, MD 20852

Re: Docket 01D-0368

Dear Docket Management Branch:

We have enclosed our comments on the CTD Guidance document published in the Federal Register on September 5, 2001. We e-mailed our comments to your branch on November 5, as the deadline specified, but we are concerned you may not have received it.

We are co-chairs of a committee that is part of a drug development professional society, and are focused on facilitating globally harmonized Medical Writing. We polled our members and consolidated their comments on the guidance, into one document, which is enclosed.

Please feel free to contact any of us with questions.

Sincerely,



for:

Janet Ehlert, Director, Clinical Documentation, Organon Pharmaceuticals Inc. (973 325-5231)

Sandra J. Hecker, RAC, President, Hecker & Associates, LLC (703 294-4933 or 240 683-3173)

Jean Soul-Lawton, DPhil, Director, Submissions Development, GlaxoSmithKline Research and Development (44 [0] 181 422 3434)

Linda F. Wood, RN, MPH, President, MedWrite, Inc. (978 692-2369)

01D-0368

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Background Information

Through one of our professional associations, we solicited medical writers who work for pharmaceutical, biologic, and device companies, academic and research institutions, and CROs and CSOs, and medical writers who are independent contractors to submit comments on the *Draft Guidance for Industry, "Submitting Marketing Applications According to the ICH-CTD Format – General Considerations"* [Docket No. 01D-0368]. In general, we thought the guidance was well written. We believe one or more FDA meetings to address implementation of the guidance will help prevent the confusion, incorrect interpretation, and inefficiency that resulted during implementation of the ICH E3 guideline.

Before we address specific comments on the content, we want to state for the record that we noticed and appreciated the efforts FDA made to ensure the guidance was so well written. Those of us who have been reading guidance for many years observed that this guidance was remarkably free of typos, and was very clear, and well-organized.

We received two types of comments:

- 1) Requests for clarification of specific points in the guidance and
- 2) Observations about FDA requests that may be difficult to meet or may perhaps have unanticipated adverse effects on the writing, dossier publishing, and review process.

Section I.

Several medical writers suggested stating here that this guidance primarily addresses paper CTDs and that electronic CTDs are discussed briefly in Section V.

(There were no comments on Section II.)

Section III.

Several medical writers requested that "document" be defined more clearly. (Some writers believe "document" now means what "section" used to mean.)

III A 2.

Clarification is requested as to how the table of contents should look. Would it be a list of contents and their corresponding tab text information along the right hand margin of the list, in place of page numbers? How many subsection levels would be expected in the table of contents? (For every level that has a tab identifier?)

There was much concern about the large number of tab identifiers that will be required in paper submissions to meet FDA's requests in this guidance. Inserting tabs is often a manual process and many medical writers thought that the CTD format guidance will

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result in “a sea of tabs” that, together with the lack of overall CTD pagination, will make it difficult for industry and FDA alike to navigate section hierarchies easily in these massive documents. We discussed among ourselves whether one alternative might be the use of colored slip-sheets to separate sections of a document (e.g., text of a clinical study report [CSR], from its individual tables, appendices, and listings) that FDA is now requesting be regarded as a series of documents.

Clarification is also requested for tab content, e.g., for a tab for literature reference article, would “ref 5” be adequate or does FDA prefer the author(s) and short title be listed on the tab?

III B 1.

This section describes the overall table of contents. Should this be a duplication of the Table of Contents cited in III A 2. (excluding Module 1)? Or does FDA want to see a different level of detail in the Table of Contents here? (If so, more or less detail?)

III E.

It is implied, but not specifically stated, that CSRs should still be compiled according to the existing ICH E3 format. The sections on case report forms (CRFs), individual patient listings, and literature references need to be clarified so that these sections of the CTD are not redundant with information in the CSR appendices. Specifically, based on the electronic submission guidance issued in 1999, we do not believe that it is FDA’s intent to have such information appear twice in the CTD (i.e., as report appendices in the CSR *and* separately as individual documents in the CTD grouped by study under the separate headings of, e.g., CRFs or literature references). The wording currently stated in the guidance may lead some individuals to provide CRFs, literature reference articles, and other appendices both as part of CSRs and in separate locations in the CTD. A related issue is that if the CRFs and other items appended to a CSR are to be placed somewhere other than in the CSR appendices, some medical writers were concerned that the CSR would no longer follow the ICH E3 guideline. Clarification of this issue in the draft guidance would be helpful.

The guidance also states, “You should include any case report forms (CRF) as separate documents. The case report forms should be organized by study.” Per ICH E3, Appendix 16.3 of the CSR only contains CRFs for deaths, other serious adverse events, or withdrawals for adverse events (Appendix 16.3.1) and “other” CRFs submitted (Appendix 16.3.2). Some medical writers questioned whether this section of the CTD was meant to include all CRFs for *all* patients?

III E 2.

The issue of whether an ISE and/or ISS is needed has arisen at many industry meetings. It has been communicated at such meetings that extensive analyses to support the Summary of Clinical Efficacy and the Summary of Clinical Safety should be not provided in Module 2 and that when extensive analyses are prepared for an application, a report of some kind needs to be placed in Module 5 and summarized in Module 2. It would be helpful if wording could be added to the draft guidance to assist industry in determining

appropriate placement of the analyses traditionally associated with such documents as the ISE and ISS.

Section IV

IV A.

FDA states “We will consider, on a case-by-case basis, accepting submissions where some modules are provided in the CTD format and the rest of the submission is not in the CTD format.” Some medical writers expressed concern that this contradicts FDA’s publicly stated position, that mixed CTDs will be accepted as long as at the module-level format is consistent (completely CTD or MAA or NDA). The EU and Japan are accepting mixed-format CTDs. If FDA’s position differs from that of the EU and Japan, then considerable rewriting of a dossier could be required in those cases where FDA does not accept a mixed-format CTD. This seems to defeat one of the key objectives of the CTD. We suggest that the sentence be revised slightly, e.g., “We will accept submissions where some modules are provided in the CTD format and the rest of the submission is not in the CTD format. However, the sponsor needs to communicate this to the FDA.” (It would also be helpful to specify when.)

IV D.

Would FDA accept a CTD submitted on A4 paper? Some of the medical writers at companies with less advanced word processing capabilities but who are submitting global marketing applications noted difficulties, e.g., with complex tables, in republishing applications on different sizes of paper.

IV E.

A left margin of 0.75 inches does not seem wide enough to see the text on the left margin of a bound volume. A number of medical writers commented that 1.5” (3.65cm) is the usual minimum for the left margin. We recognize the flexibility of FDA in establishing a minimum requirement for the left margin, but suggest that FDA should perhaps establish the minimum left margin at a measurement reflective of actual practices. Also, some writers questioned whether 0.25 for the other margins was wide enough, if, for example, a reviewer wanted to write on the pages.

On a related note here and to IV D. above, medical writers suggested that it would be helpful if FDA stated measurements in metric units as well as in US units to assist those compiling applications in other parts of the world.

IV F.

Arial 11 point is popular in publishing groups in our industry, and writers at specific companies have noted that multiple marketing applications have been accepted by FDA in Arial 11 point—could it be stated in the guidance that Arial is also acceptable?

Clarification was requested of a statement in the guidance that seems internally inconsistent: “Generally font sizes 9 to 10 points are considered acceptable in tables but you should avoid fonts smaller than 12 points whenever possible.” We wondered if “in text” should be added to the sentence after “12 points.”

IV G.

Some of our experienced submissions experts understand that the different sizes of the front and back covers of volumes facilitate FDA handling of the volumes. But other medical writers have worked for multiple companies and have only submitted volumes with the front and back covers the same size without comment from FDA. Several medical writers expressed concern that the uneven front and back covers would cause volumes on bookshelves in company archives to fall apart more readily. Others were concerned that novice pharmaceutical staff will interpret this guidance as a requirement. Could FDA clarify that, while the binder cover sizes specified are preferred, same-size front and back covers will be accepted?

IV K.

Some medical writers wanted clarification that if only one page number is to be on each page, it should be the original document (e.g., original protocol) page number since many of these are legacy-controlled documents and any change to them requires documentation and republishing.

Another concern was if each subsection of a CSR or section has its own page numbering, it may be confusing and time-consuming for regulatory reviewers and industry staff alike to navigate the many volumes associated with a paper CTD without a numbering hierarchy to guide them.

IV M.

There was puzzlement about the specified box size. One member measured 3 different brands of banker boxes, which her company uses to send marketing applications to FDA, and found all three measured 15 x 12 x 10 inches. This is the box size also reported to be used by other medical writers in the past when submitting applications to FDA. If the box size specified in the guidance is the ideal, we suggest wording be added to convey that submission of applications in banker boxes 15 x 12 x 10 inches in size also is acceptable.

Section V.

We suggest a reference to this section at the beginning of the guidance document; this will help orient the reader to that fact that many of the conventions in the guidance pertain to a paper submission but that those interested in filing the CTD electronically can refer to Section V. One member suggested adding a mock table of contents as seen on p 41 of the guidance "Providing Regulatory Submissions in Electronic Format – NDAs."

If you have questions about our comments, or would like more information about any of the points we raised above, we would be happy to talk with you. Please feel free to contact any one of us.

Sincerely,

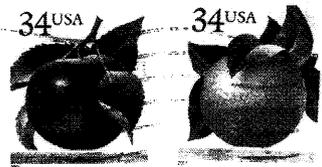
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