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ASSISTANT VICE PRESIDENT
INTERNATIONAL REGULATORY AFFAIRS

PhRMA

November 5, 2001

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
rm 1061
Rockville, MD 20857

Re: Draft Guidance for Industry on Submitting Marketing Applications According to the ICH/CTD Format; General Considerations, Docket Number 01D-0368, 66 Federal Register 46464, September 5, 2001

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies that are devoted to inventing medicines allowing patients to lead longer, happier, healthier and more productive lives. Investing $30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for new cures.

I am writing on behalf of PhRMA to provide comments on the *Draft Guidance for Industry on Submitting Marketing Applications According to the ICH/CTD Format; General Considerations.* PhRMA believes that the introduction of the CTD, a major ICH accomplishement, in the US, Europe and Japan will significantly streamline the processes companies undertake to file New Drug Applications in these three regions. From this standpoint the FDA's General Considerations document is a key element in ensuring the smooth implementation of the CTD, and we would like to ensure that as this guideline is finalized, the following comments, which constitute clarifications in the text, or raise issues that may not have been fully addressed in the Draft Guidance, are taken into consideration.

The enclosed attachment summarizes PhRMA's comments on this document. We trust that these will be useful to the Agency as this draft guideline is revised.

Sincerely,

Cloew

01D-0368

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General Comments

PhRMA would like to commend the FDA for developing a comprehensive guidance to support the implementation of the International Conference on Harmonisation (ICH) Common Technical Document (CTD). We have several general comments:

1. PhRMA recognizes that there are several relevant guidance documents on the CTD, and recommends that the FDA General Considerations document indicate the inter-relationship of these documents for clarity, as well as the intended purpose and scope of each document.

2. PhRMA would like to see the FDA's General Considerations document more forcefully support and encourage the submission of dossiers in CTD format. While PhRMA appreciates that the CTD will not be mandated until simultaneous rule-making is initiated and completed for the electronic and paper CTD formats, we feel nonetheless that the addition of language to the General Considerations document similar to that used in the European Guidance Volume 2, Notice to Applicants, Volume 2B, 'Presentation and Content of the Dossier Common Technical Document (CTD)', July 2001 ('Companies are encouraged to use and switch to the CTD-format as soon as possible') would be appropriate.

3. In the General Considerations document the FDA recommends that sponsors 'regularly' submit dossiers in CTD format by 2003. PhRMA would like to suggest that FDA clarify this to indicate 'July 2003' as agreed by the ICH Steering Committee (Tokyo, May 2001), and that the reference is specific to new applications. PhRMA also interprets 'regularly' to mean 'ordinarily', ie unless with prior Agency agreement that a non-CTD format is not acceptable unless the sponsor has prior Agency agreement. As in point 2 above, this simply reflects the status of rule-making on this issue.

4. The General Considerations document clearly applies to NDA, ANDA, and BLA submissions, as well as all subsequent submissions to such applications. The document also clearly states that a company may use the CTD format even if the original submission was not in CTD format, although PhRMA recommends this statement qualified to indicate that use of CTD format is optional in these circumstances. PhRMA also recommends that FDA to consider extending the scope of the CTD to apply the general organizational structure and electronic principles to INDs.

5. The General Considerations document indicates that Case Report Forms and Individual Patient Listings are to be provided in a separate section of the CTD, Module 5, 5.3.7. Case Report Forms and Individual Patient Listings. In light of this PhRMA recommends that the ICH E3 Guidance "Structure and Content of Clinical Trial Reports" be modified. This guidance currently contains two appendices, Appendix 16.3 Case Report Forms, and Appendix 16.4 'Individual Patient Data Listings (US Archival Listings), which the General Considerations documents suggests could be eliminated. If such an amendment is possible, PhRMA recommends that FDA initiate the appropriate ICH processes.

6. The CTD uses the word 'quality' in place of 'chemistry' used in other FDA guidances. PhRMA recommends that FDA clarify whether the CTD-related guidances will impact the standard information found on current NDA binder covers as found in the FDA binder specification, http://www.fda.gov/cder/ddms/binders.htm.

7. PhRMA recommends that the FDA coordinate with the EU and MHLW with regard to certain style issues, such as volume covers, colors used, margin size and font type and size. Specifically, significant regional deviations from a common format may significantly impact the dossier preparation process, and make the CTD less 'common' to all three ICH regions. Furthermore, PhMRA recommends that FDA clarify whether attachments and scanned documents will have to follow the prescribed format.

Specific Comments

The following comments refer to specific sections of the General Considerations document, and are reference by page and section number:

Page 4, Section III.A.: Module 1 - Administrative and Prescribing Information

A footnoted reference is made to the cover letter, "Applicants often choose to submit a cover letter with their submissions. If you plan to include a cover letter, it should be placed at the beginning of Module 1."

PhRMA considers that it is typical for sponsors to submit a cover letter with an application. Furthermore, guidance from both CDER and CBER on electronic submissions gives clear instruction to the sponsor to provide a cover letter to include specific information. In future electronic CTDs, both sponsors and FDA will find it useful to have cover letters included in the XML DTD specification for Module 1. PhRMA therefore recommends that the cover letter move from a footnote to a text specification as the first document in Module 1.

Page 4, Section III.A.3.a.: Administrative Documents

Federal Regulations require that the order of the documents in a submission follow the order indicated on the 356h form. PhRMA notes that this is currently inconsistent with the requirements from Electronic Common Technical Document FDA Regional Information, July 3, 2001, Page 7. PhRMA recommends that the FDA modify the requirements from Electronic Common Technical Document FDA Regional Information, July 3, 2001, Page 7 to ensure they are consistent with this document and the 356h form.

Page 5, Section III.A.3.a.: Administrative Documents

Environmental assessments are sometimes full reports, not just administrative requests for categorical exclusion. Since the guidance states that the environmental assessment should be submitted in a separate volume, it should not be listed with the administrative documents. To not disrupt the numbering flow of the documentation, a logical place in the guidance to include the environmental assessment is at the end of Module 1. By using such a document order, the individual technical reviewers will be able to receive copies of administrative documents and labeling in one volume, while the chemistry reviewer can receive an additional volume containing the environmental assessment report.

PhRMA notes that the European CTD implementation guidance places the environmental assessment at the end of Module 1 as an annex (appendix), in line with our suggestion.

Page 7, Section 2: Study Reports and Related Information

'The submission of a separate ISE and/or ISS is not required when the information provided can be incorporated into the CTD summaries and overview.'

PhRMA recommends that FDA provide a more detailed mapping of where information from ISS and ISE should go in the CTD format because it would be very beneficial for sponsors compiling a CTD.

Page 9, Section 2: Review Copy

'It is recommended that you contact the office with the responsibility for the review of your product to determine how many copies of each module or sections of modules should be submitted.'

This statement suggests that the number of review copies is no longer standard, but to be decided by the review division. PhRMA suggests that this could lead to a sponsor potentially having to supply more review copies, rather than less, and instead recommends reinstitution of a standard required number of copies.

Page 12, Section IV.K: Pagination

"If you include a document within a document, such as a protocol within a study report, the document to be included (in this case, the protocol) should be attached as an appendix. You should demarcate each appendix with an appropriately named tab identifier."

PhRMA recommends that the Agency confirm its intent, with this statement, that there would be no overall page numbering required for, say a Clinical Trial Report.

Page 12, Section L: Cross-Referencing Documents

"You should reference documents by volume, CTD module, tab identifier, and page number."

PhRMA notes that there is a slight difference here between European and US guidance:

NOTICE TO APPLICANTS Volume 2B 'Presentation and Content of the Dossier Common Technical Document (CTD)', July 2001, foreword & introduction Page 10: "Cross-referencing to documents should be made by referring to the volume number and section, followed by the page number (e.g. see Module 3, Vol. 6, P.4.3 Method Validation, p 23)."

PhRMA believes that the EU Notice to Applicant cross-referencing method represents the agreement reached by the ICH Steering Committee in Tokyo 2001, and recommends that the Agency amend the draft guideline to reflect this agreement.

Appendix A

PhRMA believes that Appendix A does not include all the relevant references to ICH guidances, particularly for Modules 3 and 5. PhRMA recommends that Appendix A be updated to include all relevant references, including ICH guidances.