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PhRMA

October 27, 2003

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

Re: Docket Number 2003D-0364; Providing Regulatory Submissions in Electronic Format - Annual Reports for NDAs and ANDAs; Draft Guidance; 68 Federal Register 51788

Dear Sir/Madam:

The following comments on the above draft guidance (**eAnnual Report Guidance**) are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA).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.

General Comments:

PhRMA supports FDA's desire to utilize common technologies that are consistent with the ICH electronic common technical document (eCTD). However, this document is not clear on whether the eCTD technologies are to be utilized.

It would helpful if both CBER and CDER embraced the same electronic format for annual reports for NDAs, BLAs and ANDAs.

The cover letter is not mentioned in the guidance. Can sponsors discontinue this practice?

There is also no mention of table of contents or hyperlinks.

This draft guidance would appear to be somewhat outdated. Publication nearly coincided with the release of draft eCTD guidance. One might expect that these guidance documents would compliment each other; however, these two guidance documents appear to conflict, which could easily cause confusion. Many sponsors have been producing a hybrid solution to meeting the requirement for submitting in CTD format, yet continuing to submit electronically. This annual report guidance aligns with eNDA guidance documents, with no consideration of CTD (although expected granularity is noted).

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There is no mention of IND Annual Reports; however, some guidance on granularity and location of (Module 1) IND Annual Report granules is noted in the eCTD Guidance. Consideration for inclusion of IND Annual Report Guidance is requested.

The NDA requirement for "Other reporting – Advertisements and promotional labeling" is not addressed in the draft guidance. Please address the requirement for this reporting in the draft guidance.

There are at least two separate components within the guidance, those items in the ***us*** folder, and those sections (Clinical, Labeling, CMC, Nonclinical) that are covered by the "Guidance for Industry Providing Regulatory Submissions in Electronic Format-NDAs" (**eNDA Guidance**). Why are the items defined in **eNDA Guidance** much more specific, in terms of: file naming/structure/the way the information is divided, than the documents in the ***us*** folder? We would like to see more definition, especially in terms of files names and folder structure added to the draft guidance or clarify that these can be defined by the sponsor.

In terms of the components that refer to the **eNDA Guidance**, there seem to be numerous gaps and clarifications that need to be made between the Annual Report requirements (CFRs) and the **eNDA Guidance** sections that are referenced. It might be helpful if the requirements referenced in the **eAnnual Report Guidance** referred to specific parts/sections of the **eNDA Guidance**, rather then the document as a whole. Why didn't FDA choose to write give specific guidance based on Annual Report requirements?

Specific Comments on the Draft Guidance

I. Introduction

On line 21, change "...regulatory submissions in electronic format..." to "...regulatory submissions in eCTD format..."

II.A. The Archival Copy

In lines 47-54, the paragraph related to the archival copy is unclear. The last sentence should state, "you should not provide any documents in hard copy except for those documents that require an original signature" instead of "an electronic signature".

III. Organizing the Submission

In lines 67-71 it indicates that the "Reports for ... should be organized as described in the guidance for industry on *Providing Regulatory Submissions in Electronic Format — NDAs* or as described in the guidance *Providing Regulatory Submissions in Electronic Format — ANDAs*." Does this mean the submission should be organized by item as with the NDA and by the eNDA folder structure? This is confusing since the "Attachment The eCTD Document Information Backbone Files Specification for Module 1" also supports a submission-type="annual-report" parameter. If the intent is to have Annual Reports submitted in eCTD format then this should be explicitly stated in the guidance.

In line 66–72, PhRMA is unsure if the CMC Summary/section is to be placed in the **us** folder and everything else follows the CMC structure. We currently have an overall summary at the beginning of the Annual Report that includes CMC information. The guidance doesn't address this but instead specifically discusses the CMC section. Is this summary still required?

In lines 66–72, provide instructions for eCTD submissions, e.g. documents for the annual report should be organized as described in the guidance for industry on *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions*. Information for chemistry, manufacturing, and controls (CMC) (§ 314.81(b)(2)(iv)) should be placed in a folder named m3. Reports for nonclinical (§ 314.81(b)(2)(v)) studies should be placed in a folder named m4. Reports for clinical studies (§ 314.81(b)(2)(vi)) should be placed in a folder named m5. All other documents for the annual report should be placed in a folder named m1.

In lines 71-72, it is unclear whether the Labeling section should be in the ***us*** folder or "organized as described in the **eNDA Guidance**" (lines 105-106).

In line 74 – 75, it is not clear how the suggestion to provide 2252s as a single file would apply to moieties. For moiety submissions sponsors currently send the full annual report under the primary NDA and send all others as "cover letter only" referring the agency to the full submission referencing the primary NDA number. For electronic NDAs, it's not clear how to proceed. Is there a way sponsors can include all of the 2252's associated with all relevant NDAs under the primary submission? If so, would sponsors be able to put multiple PDFs in the "*us*" folder? If not, do sponsors send in separate electronic submissions for all NDAs referring back to the primary. This would be individual CD's with one PDF (Form 2252) on them, which seems inefficient. Please clarify.

On lines 81 – 85, please provide instructions for eCTD submissions. For example:

81	appropriate nonclinical studies	m1-13-1-summary-nonclinical-studies
82	clinical pharmacology	m1-13-2-summary-clinical-pharmacology-information
83	safety	m1-13-3-summary-safety-information
84	labeling changes	m1-13-4-summary-labeling-changes
85	other significant new information	m1-13-7-summary-other-significant-new-information
		m1-13-5-summary-of-manufacturing-changes
		m1-13-6-summary-of-microbiological-changes

On line 95, please provide instructions for eCTD submissions, e.g. m1-13-11-distribution-data.

On lines 96-97, please provide instructions for eCTD submissions, e.g. m1-13-14-log-outstanding-regulatory-business.

On lines 99–103, please provide instructions for eCTD submissions, e.g. m1-13-12-status-postmarketing-study-commitments, m1-13-13-status-other-postmarketing-studies.

On lines 105–107, please provide instructions for eCTD submissions, e.g. m1-14.

All other guidance documents use NXXXXX as the main folder. Since there is no mention of this, do sponsors do so to be consistent or is that eliminated in this submission type?

Again, we appreciate the opportunity to comment on the details of the proposal, and applaud FDA's initiative to implement the eCTD.

Sincerely,

Alan Goldhamer