

# Bristol-Myers Squibb Pharmaceutical Research Institute

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29 July 2002

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

**Re: Docket No. 01D-0435; Draft Guidance on Electronic Common Technical Document Specification [*Federal Register / Vol. 67, No.115 / Friday, June 14, 2002*]**

Dear Sir or Madam:

Bristol-Myers Squibb (BMS) is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2001 alone, Bristol-Myers Squibb dedicated \$2.1 billion for pharmaceutical research and development activities. The company has nearly 6,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises more than 50 compounds under active development. For these reasons, we are very interested in and well qualified to comment on this FDA Guidance on the Electronic Common Technical Document (eCTD).

We would like to commend the U.S. FDA for their lead role in embracing the CTD format and their continued global leadership in the acceptance and utilization of electronic submissions.

In reviewing version 2.0 of the eCTD specification, we find there are aspects which still require clarification and/or further specifications which until provided, would make preparation and implementation as well as review of the eCTD difficult. There are four main areas that we wish to comment upon at this time:

- 1) keeping specifications for the dossier distinct from specifications for documents,
- 2) the need for further standardization and specifications on the submission of documents as multiple files,
- 3) creating specifications for providing a document that supports more than one section of the eCTD, and
- 4) standardizing the specifications across regions for providing data in support of documents.

01D-0435



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## **1) Dossier Specifications versus Document Specifications**

It is stated in the Process section of the specification that the Change Control Board (CCB) will publish changes to the specification on at least an annual basis and that regulatory authorities will support submissions described by at least two consecutive versions of the eCTD specification. Considering the development time of a product, it seems that even if the specification changed only once a year, it is possible that dossiers may contain documents which were finalized on specifications of greater than two years (or versions) ago. Thus, it is important to distinguish specifications related to the order (or organization) of documents in the eCTD structure versus specifications related to the format and/or granularity of the individual documents themselves. Support for aspects of the specification that impact the granularity and/or format of documents would need to be in place for greater than two years (or versions). It is therefore suggested that document granularity specifications be managed separately from dossier specifications. Separate specification management (document vs. dossier) will also make it easier to evolve document level specifications (e.g., moving toward XML documents rather than PDF) without having to modify the eCTD dossier specifications.

## **2) Further Standardization and Specifications for Documents Provided as Multiple Files**

Additional standardization and specifications are requested in sections where there is an option to submit documentation as a single file or as multiple files. The current lack of specification in the submission of a document as multiple files will make reviewing more difficult as each sponsor will provide documentation at a slightly different level of granularity. Leaving the specification open to regional interpretation may create the situation where each region has unique specifications which would thus require industry to create more than one version of the same document in order to comply with different regional preferences, further contradicting one of the primary goals of the CTD. Providing global specifications on granularity, naming, foldering and file size restrictions will benefit both sponsors and reviewers.

As an example, the Guidance indicates that study reports in Module 5 may be submitted as a single file or as multiple files. Global specifications for submitting in the multiple file approach should be attainable using the organization and naming of files in accordance with the ICH E3 Specifications. Each region would thus be free to identify which of the standard files are required to be submitted in their regional guidance.

## **3) Using a Single Document to Support Multiple Sections of the eCTD**

Additional specifications are requested on how documents that support more than one subsection of the dossier are to be cited in the XML instance without requiring the inclusion of the document multiple times. There are many instances where the same document (or file) may be applicable in multiple subsections but no standard is provided on how this should be done. While the XML instance could reference a document multiple times, the folder/file view of the dossier would not show the existence of that file in that specific location and would give the impression that no information was provided.

For example, in Module 3, additional clarification is needed in the specification for Section 3.2.P where it is requested that the submission of drug product information be 'by strength' (e.g., 'tablet 5mg'). Requiring this level of reporting granularity for each of the subsections of 3.2.P

(i.e., sections 3.2.P.1 through 3.2.P.8) will add tremendous redundancy and repetition to this section of the dossier as well as additional burden to the sponsor for the generation of documentation in this manner. In many instances, a document may support all strengths and the inclusion of this document multiple times seems contrary to the objectives of the eCTD and XML functionality.

A similar situation arises in Module 4 with respect to the submission of pharmacokinetic information where the granularity of ADME study report documentation does not generally follow the specification. The specification implies that individual documents will need to be created presenting the absorption, distribution, metabolism and excretion of a drug. In practice, it is common to conduct one study (and create one report) to describe some or all of these aspects of the drug's pharmacokinetics. Thus, one document may describe the absorption and excretion of a product in a specific species. Additional clarification or specification is thus needed on how to utilize this one document in support of multiple sections of the eCTD without including the document multiple times.

#### **4) Provide clear specifications for providing data in support of documents**

In each of the technical modules, the specification needs further clarification on the submission of "data" in support of study report documents. The submission of "data" is generally interpreted to mean the submission of data as a data file (SAS Transport), so it is confusing when data is referred to in PDF format. Further specifications are requested on the format and organization of the "data" elements cited in the specification for each Module.

There is also a lack of consistency in the specification with respect to the submission of data. Appendix 4 indicates each study report document in Module 4 may be submitted as multiple PDF files (a report.pdf and report-data.pdf file); the Appendix does not provide for the same level of granularity at the study report level in Module 5. This should be implemented consistently across modules and better defined. As discussed above in 2), the granularity of documents to be submitted as multiple files should be standardized across regions, with regional guidance identifying which of the files are required to be submitted.

Additional specifications and guidance are also requested in the specifications for Module 3, specifically relating to the submission of Batch Records and Methods Validation as well as specifications on the content and format for the submission of data files in support of these sections.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



Laurie Smaldone, M.D.  
Senior Vice President  
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