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Global Research & Development

February 25, 2002

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

RE: ICH Draft Guidance, Electronic Common Technical Document Specification
(e-CTD)
Docket No. 00D-0435, 66 Fed. Reg. 229 (28Nov2002)

Dear Dockets Management:

Pfizer Inc submits these attached comments on the **ICH Draft Guidance, Electronic Common Technical Document Specification (e-CTD)**, published in the *Federal Register* on November 28, 2002.

We thank you for this opportunity to comment on this Draft ICH Guidance document.

Sincerely,

William R. Murphy, Ph.D.
Senior Associate Director
Pfizer Global Research and Development
Worldwide Regulatory Affairs

Att:

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Recommendations from Pfizer Inc for the ICH M2 EWG – Electronic Common Technical Document Specification
V1.0 24 June 2001
Issued in the *Federal Register* November 28, 2001

| # | Section of document | Description of Change/Comment | Reason for Change/Comment |
|---|---|--|---|
| 1 | Table of Contents, Page 2 | Add the following within the TOC- Formats.....2-2 Links.....2-4 Presentation.....2-4 Element to file directory mapping.....2-5 Character encoding.....2-6 Pharmacology.....7-4 | Missing. |
| 2 | Appendix 1, Overall Architecture, Page 1-2, Paragraph 2 | The referred to “standards style sheet” indicates this as being defined and provided by the ICH-M4 EWG. Specify if this is in its final format. | This will help clarify usage and anticipated change to start using this. |
| 3 | Appendix 2 The eCTD Submission, Page 2-2, Subheading “Formats” | The first sentence reads “Formats should be readable at least for as long as it is needed for the regulatory process”. What thoughts are there to maintain readable format over such a long period of time, and possibly include maintenance requirements within this specification. | This process can be extremely long (e.g. 50 years or longer in the case of possible legislative requirements). Therefore the management of records and systems over this length of time is a major concern; this impacts (1) application versions of existing software (PDF readers, XML editors), (2) operating systems/hardware/ application products (systems, drivers, vendor products), and (3) physical output media (diskettes, CD_ROM, DVD) |
| 4 | Appendix 2 The eCTD Submission, Page 2-4, Subheading “Links” | Changes to the 1 st paragraph highlighted below. <i>“Links among objects in the eCTD Submission should be relative. The intention is to make the eCTD Submission self-contained. All literature references introduced by the sponsor should be included in the submission, for secondary references (references to a reference), absolute links to external objects may be used. There could be absolute links to other external objects. These would probably be references.”</i> | Inclusion of ALL types of references is overwhelming work for study reports. Only appropriate references to be included, as highlighted in the changed sentence. |
| 5 | Appendix 2 The eCTD Submission, Page 2-4, Subheading “Presentation” | Provide clarity on the statement “For example, there could be one presentation for the screen and another for the paper.” | This wording makes it appear that there is not a guarantee in the fidelity of the files, and there is a need to increase the Quality Control efforts to ensure integrity of the information provided. |

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| 5 (Cont'd) | Appendix 2 The eCTD Submission, Page 2-6, Subheading "Name"; Appendix 3 File Organisation for the eCTD; Appendix 6 Module 3 Quality; Appendix 8 Module 5 Clinical Study Reports | Appendix 2, Appendix 6, and Appendix 8 indicate that a maximum length of a Directory or a File Name is 256 characters. Appendix 3 limits the Folder and File names to 32 characters. Please clarify the appropriate length. | Clarity regarding what file/folder name lengths should be provided. |
| 6 | Appendix 3 File Organisation for the eCTD | The Appendix in the June 2001 version is very detailed as opposed to the November 2001 Word file that was briefly available. The June 2001 version seems much more detailed and adequate for adoption. | The most detailed version is preferred. |
| 7 | Appendix 3 File Organisation for the eCTD | Map the eCTD elements to the CTD numbering schema. For example Schema Number 2.7 has element name "m2-7-clinical-summary". This maps to the directory "clinical_summary". These are not all consistent. | This makes it easier to automatically create folders when making an eCTD submission at the pharmaceutical sponsor. This would also make the names unique and shorter. |
| 8 | Appendix 3 File Organisation for the eCTD | Have naming conventions for all files (leaf nodes) with a scheme that has multiple parts. For example- (a) <i>CTD number</i> : 2.7.1 (b) <i>Document Type</i> : (based on a defined list) (summary, study report, etc.) (c) <i>Date Submitted</i> : 02202002 Furthermore, restrict element names to solely the module identifier part (m2-3-1) and the title/name to be designated by a different unique, fixed attribute. | This makes for easier identification and compilation. It allows for each attribute field to describe only one item. This separates locations, names, and adds additional useful attributes. |
| 9 | Appendix 3 File Organisation for the eCTD | The specification should use unique file and directory naming conventions across all of the different documents and folders specified. | This specification has several files that have the same file name (e.g., 2.6.2.1 and 2.6.6.1 both have a file named brief_summary.pdf). To ensure non-conflicting possibilities during searches or automated linking tools, it would be best to have all names unique. Particularly important is the cross linking from within PDF files. |

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| 10 | Appendix 3 File Organisation for the eCTD | Full acceptance and clarity within the specification of subdividing files into their constituent parts. We suggest it would be best to subdivide all Module 2 files into their constituent parts. | Appendix 3 identifies several sections that can be submitted as one entire file or subdivided into constituent parts (e.g. 2.3, 2.7.1, 2.7.2). Subdividing facilitates locating specific sections of the document and therefore the review. Additionally, revisions made to one subdivision will not require resubmission of the entire file, but only the subdivision(s) affected. |
| 11 | Appendix 3 File Organisation for the eCTD | The CTD Numbering Schema to be completely numeric versus a mix of numeric and alpha characters. | This would assist in a clearer schema for following the appropriate ordering of documents. It would also assist in the item listed below in regards to unique references and appropriate sequencing of documents (See #12 below). |
| 12 | Appendix 5 Module 2; Appendix 6 Module 3; Appendix 7 Module 4; Appendix 8 Module 5 | Include within the file name the actual corresponding numerical sections (e.g., 2.6 nonclinical_summary; 2.7 clinical_summary, etc.) | Appendices 5-8 make reference to the "nature of the operating system" which lists the folder hierarchy in alphabetical order - which is therefore not in sequence with the CTD. With this limitation in mind, it would be beneficial to have various files in the folders identified with their corresponding numerical sections, which would then appropriately list them in the proper sequence. |
| 13 | Appendix 9 Transmission and Receipt | Pending the use of the ESTR1 gateway, the process of archiving the physical CD-ROM/Tapes containing the submissions should be clearly defined once the regulatory agency has uploaded the information to their database. | This is unclear in the guidance, being that there is no additional security mechanism (such as passwords) allowed to be applied to these. This would also assist in unique naming mentioned above in #7. |
| 14 | Appendix 10 Preparation of the eCTD, Subheading "Background", 3 rd paragraph. | Instead of not allowing empty folders, it is favorable to include an empty folder and have a Not Applicable description assigned. | This would clearly distinguish between "no data" and inadvertent "omission of data". |
| 15 | Appendix 10 Preparation of the eCTD, Subheading "Background", 5 th paragraph. | Insignificant to qualify the links as "downward". | In this paragraph links are described as "...and links will be downward within a module." As links are not usually directional in nature, this qualification is unnecessary. |

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| 16 | Appendix 10 Preparation of the eCTD, Page 10-3, Figure 10-1 | Put more details and clarity into this diagram. There are many areas that can be addressed in more detail. In particular, include the cross document linking. | There is not a lot detail for what is an extremely important piece of the submission. |
| 17 | Appendix 11 Creating the eCTD XML Submission, Attribute "operation" | Within the "operation" row, the "description/instructions" column references the replacement and deletion of files. Please clarify the process of resubmitting this type of information (as well as the new data), as there are security concerns with talking about deleting and replacing already submitted data. | There seem to be 2 issues surrounding this (1) security – ability to delete or replace files at the agency should be controlled with the use of access control list or permissions to avoid the inadvertent deletion of data. (2) this would ultimately affect the previously submitted metadata and checksum associated with the original submission. |
| 18 | Appendix 12 Specification for PDF, Subheading "Introduction", Page 12-1, 1 st paragraph | Indicate actual numbers within the statement "...documents defined within Appendices x to x of this specification." | Appendices references not given. |
| 19 | Appendix 12 Specification for PDF, Page 12-2, "Source of electronic document" | This statement indicates "scanned documents...do not allow...copy and paste text for editing". Note this is not true. This functionality can be applied by "capturing" the pages once they have been scanned into PDF format. | Incorrect statement regarding copying and pasting text. |
| 20 | Appendix 13 Specification for XML Files; Appendix 1 Overall Architecture | Clarification made between the acronym "DTD" that is used both in Appendix 1 and Appendix 13. In Appendix 1 it is defined as "Document Type Definition" and in Appendix 13 it is defined as "Document Type Declaration". Indicate if these are intended to be different or the same. | The " <i>Document Type Definition</i> " is described as being what the XML backbone must be designed and validated according to. The " <i>Document Type Declaration</i> " is described as being the file in which the specific names of the element types and attributes, as well as the valid syntax, structure and format for defining the XML elements are stored. |
| 21 | Appendix 15, Glossary | Add definitions for the acronyms W3C, EDI, CAD, CCITT | This is helpful to understand as these are important terms used within the document |
| 22 | General, across all sections | Follow a consistent terminology throughout the use of the document. | It is at times confusing to following the document when different words are used to mean the same thing. For example, sponsor is referred to as the "applicants, submitter, and sponsor" throughout the document. |

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| 23 | General, across all sections | A proofreading to be conducted of the specification is recommended. There were many formatting, grammatical and spelling errors throughout the document, as well as inconsistent use of language between British and US spellings. | |
| 24 | Undefined within the sections | Within the eCTD, specify where additional acknowledgements, amendments, and requests be placed when requested during the review of the CTD. A potential section could be the Regional Information section in Module 1. | The regulatory agencies submit acknowledgements, clarifaxes/amendments and requests to industry during the course of the review of the CTD; however, the exact section as to where these documents will be maintained in the eCTD is not specified. |
| 25 | Undefined within the sections | In regards to correspondence with the regulatory agencies – It can be interpreted that clarifaxes/amendments are considered reports, and therefore require a table of contents with links to the responses. When information from the original eCTD is being referenced in this case, please indicate which should be done – (1) have links within the response directed to information in the original eCTD or (2) make direct references only within the response. | Clarification on submitting responses to ensure they are compliant is necessary. |

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