



**liquent**

July 31, 2002

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

RE: [Docket No. 01D-0435]

Dear Sir or Madam:

Attached, please find Liquent's comments on the proposed electronic Common Technical Document specification.

Liquent provides submission assembly and management software and services to over 70 life sciences organizations filing marketing authorization applications around the globe. Liquent is in the process of developing various products and services to support its customers in leveraging the advantages inherent in the Common Technical Document. As part of that development process, Liquent invited its customers to participate in weekly electronic meetings to discuss issues and challenges around the adoption of this new specification. The comments provided herein represent the concerns of Liquent as well as a cross-section of over 50 regulatory operations personnel across 32 companies.

The comments take the form of suggestions for modifications to the specification as well as requests for clarification. It is our hope that each comment submitted will be addressed in some manner similar to the preamble to a final rule when it is published in the *Federal Register*. Great care and attention was taken in providing as much detail as possible for each of the comments. However, in the event that there is a question or clarification is required, please feel free to contact me.

Thank you for the opportunity to provide input to this very important specification.

Sincerely,

R. Richard Dool  
President and CEO

Attachment

01D-0435

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An Information Holdings Inc. Company

## ICH eCTD Specification Comments

#	Priority	Description	Risk	Affects	Solution
1	High	Technically incorrect 'relative file path' example is shown in specification text example.	Specification too vague on modified-file string formatting, causing viewer application to not work when linking to modified-file.	Specification text, e.g., exact syntax of path placed in href and modified-file attributes	Correct example shown in specification; require technically correct relative path usage.

The specification states that file paths in the XML instance should be relative from the XML instance location. (Specification p. 2-1 "One of the files in the submission sequence directory is the instance... which is the starting file for the processing by an XML processor.") Correct sponsor use of relative paths is critical expectation when coding style sheets or other types of viewing applications. However, in the example provided (on page 6-12 "instructions for an amendment, supplement or variation"), the XML snippets shown do not show relative file paths when comparing href and modified-file paths. A path beginning at 'module-2' is not relative to a path beginning at '0000'. This misalignment will cause errors when a viewer tool is used to access modified-file paths. A typical style sheet will incorrectly look for a '0001' as a child of the '0000' directory instead of as a sibling of the '0000' directory. Suggested changes:

- 1) the index file should be uniquely named and placed at the publication root (CTD1234567) and the sequence number (0000, 0001) should always be included in every href and modified-file field, or
- 2) 2) the modified-file field should include the correct relative path which includes './' prefix at beginning, or
- 3) 3) remove the statement that the paths should be relative and require the viewing technology to correct otherwise incorrect relative path information.

Liquent recommends the second option as it seems to represent the least potential impact.

#	Priority	Description	Risk	Affects	Solution
2	High	Hyperlinking in lifecycle situations	Reviewers inadvertently link to outdated files.	Specification text – provide clarification to hyperlinking and document ‘replace’ requirements.	Plan to incorporate feature in viewer product that identifies obsolete links.

Clarification is needed on how to handle hyperlinks in content documents when a document is updated (e.g. replaced). The scenario is this:

In submission 0000 there are three PDF leaf files: Document A links to Document B which links to Document C. In submission 0001, document B is replaced. There are two issues: The first is that now document A is pointed to the wrong version of document B.

It is preferred, however, that the sponsor does not have to submit a new document A simply because it has a new link. This diminishes the value of component-based updates that the eCTD specification enables. Liquent suggests that Document A not be resubmitted and that the viewer technology identify this situation and resolve it by linking to the current, correct version of Document B.

The second issue concerns the expectation for the new Document B. Is it assumed that it links back to the original document C that still sits in the 0000 directory? Does it have to rebookmark and so forth?

#	Priority	Description	Risk	Affects	Solution
3	High	Expand specification to support cross-application file references.	eCTD value of lifecycle viewing and component based maintenance are limited when applied across a product.	Specification DTD - leaf attributes and operation values	Include an additional leaf attribute to describe submission number associated with modified file field. Include an additional operation value for cross-application references.

The eCTD specification provides great value to agencies and sponsors by facilitating a view of the evolving active file. It also supports the ability to reference, not resubmit, content already submitted, reducing effort and review time. Since a product's active file can consist of multiple application types (IND, NDA, sNDA) it should be assumed that an sNDA submission may want to point to previously submitted content in an NDA submission. For example, setting the operation attribute to 'reference' to mean that a link will be provided to previously submitted file could denote this. The modified-file currently does not include the submission number field. An additional leaf attribute could be used to capture this value (*e.g.* the NDA number). This would provide enough information to allow the agency to access the previously reviewed file. This also enables complete views of the active product as opposed to just viewing information about a particular product application.

#	Priority	Description	Risk	Affects	Solution
4	Medium	Support SVG as a Narrative Leaf Format	Supporting only PDF as a Narrative Leaf Format does not meet specification goals long term.	List of Common Formats: File Format Type	Allow sponsors to provide SVG for narrative as well as graphic information.

The specification indicates (p.2-2) that "formats should be readable ...for 50 years". Desired formats are described as "neutral, standard, vendor independent, text-like", etc. However, currently the only narrative format specifically provided for is PDF. It is suggested that SVG (Scaleable Vector Graphics) is also considered for inclusion as an optional common narrative format – meaning that it is acceptable to provide SVG instead of PDF in most cases. SVG is an open W3C standard that is text-based not binary like PDF – making it a stronger eCTD content candidate than PDF based on the requirements described (archive ability and vendor independence). SVG also provides many benefits for reviewers – particularly in a web environment. Liquent would be happy to provide more information about SVG to regional authorities for consideration. Additionally, please refer to **Appendix 1** of this document for more details on SVG.

#	Priority	Description	Risk	Affects	Solution
5	Medium	Clarify use of TOC attribute values in folder names	File/folder naming is not correct on provided submissions	Specification text: Comments in Appendix 4	Clarify specification text in three places.

On page 4-9, table item #29, the comment states "The folder name should always include the indication". However, in the example being shown the folder name is "clinical-summary". It is the file name shown, not the folder name, that includes the indication. Should this say "the file name should always include the indication" instead of "folder name"? Same indication folder issue for page 4-78, item 410. There is a similar issue on page 4-17, table item #70. The folder name is body-of-data and does not include the product name.

#	Priority	Description	Risk	Affects	Solution
6	Medium	Pagination requirements and role of paper in a submission	Pagination requirements of eCTD combined with different pagination requirements for paper CTD will result in a specification that is too burdensome for widespread adoption	Specification text on pagination	Allow multiple types of pagination approaches in eCTD; allow a 'paper review copy' that matches the electronic content

It is understood that regional requirements for paper will vary. It is important for regions to recognize that requirements for paper may imply a duplicative publishing process diminishing the likelihood of eCTD submissions. A way of preventing this is to require only 'paper review copies' that are identical to the content of the eCTD. That is, the paper is produced from printing the eCTD PDF (or other content) files. This is the FDA's approach with eNDAs. Making the content the same implies that the content only needs to be published once. However, given current pagination standards (each leaf document can be separately paginated) – this approach would make paper navigation difficult. Potentially to reduce duplicative publishing effort, the eCTD submission can be paginated like a CTD submission with some additional TOC aids relating electronic file names to paper volume and page. Therefore restrictions on how the eCTD submission is pagination should not be placed in the eCTD specification. It currently suggests (p. 7-4) that pagination of leaf files is PDF-file relative ("It is easier to navigate through an electronic document if the page numbers for the document and the PDF file are the same.")

#	Priority	Description	Risk	Affects	Solution
7	Medium	Clarification of use of link-text elements and ID attributes.	These fields are not completed by sponsors, because they are not defined.	Specification text describing specifics of XML Content.	Define intended use of link-text elements and ID attributes.

The specification (DTD) allows these fields to be left blank. Until there is more clarification in their use, this is assumed to be the approach. Please clarify that this is acceptable. Please clarify intended use of these fields in the future.

#	Priority	Description	Risk	Affects	Solution
8	Low	Non-valid names used in examples.	Requirements for compliant file/folder names not clear.	Specification Text	Remove examples with low line.

Specification (p.2-5) states “low line” is not allowed in names; however, it is shown in “valid” naming examples such as “data/module\_1/introduction.html” on p.2-5.

#	Priority	Description	Risk	Affects	Solution
9	Medium	Required attribute clarification	The need for certain leaf and toc attributes.	Specification text.	Clarify use of attributes.

The requirement for certain leaf attributes is unclear, specifically: application-version, version, font-library, language, keywords. Why is the information is being requested, how will the authority be using the information, and under what circumstances are they required? Should sponsors provide this information if they are not specifically asked to by a regional authority. Please clarify.

Likewise certain TOC tags are not required by the DTD. For example, m2-3-p-drug product element has optional attributes for product-name, dosage form, and manufacturer. In addition, m2-7-3-summary-of-clinical-efficacy has an optional indication attribute. It is unclear if these need to be completed 1)always if possible 2) only if this element is repeated or 3) only if a regional authority requests it. Please clarify.

#	Priority	Description	Risk	Affects	Solution
10	Medium	Back to TOC Bookmarks.	Sponsors create unnecessary bookmarks and TOCs	Specification text.	Remove comment about back to TOC bookmarking.

P. 7. 4 states “In general, including a bookmark to the main table of contents for a submission or module is helpful”. This comment does not make sense. Since the eCTD does not have submission or module level TOCs, such a bookmark is not applicable. Please confirm.

#	Priority	Description	Risk	Affects	Solution
11	Medium	PDF Doc Info fields	Unnecessary work preparing PDF Doc Info Fields.	Specification Text.	Clarify that Doc Info Fields are acceptable, just not required.

Page 7-5 states “Document information fields should not be used for the common portions of the eCTD”. It seems the intention is that regions do not require different uses of PDF document information fields – if so that should be the statement. The wording now can be read to imply that if document information fields are completed by the sponsor for internal or legacy reasons, then they must be wiped out before submitting the PDF in an eCTD.

#	Priority	Description	Risk	Affects	Solution
12	Medium	Some attributes present in DTD but not described in specification.	Attributes are incorrectly provided or inadvertently omitted.	Specification text – TOC and Leaf attribute descriptions	Update specification text to reflect DTD.

The DTD representation on p. 6-8 does not show that the md5-checksum attribute has now been split into two attributes. Nor does it show the keyword leaf attribute. On p.6-10, keyword is not shown as a leaf attribute. Also, multiple excipient instructions are not provided and the excipient TOC tag is not discussed in the specification text but is in the DTD (on m3-2-p-4 toc tag).

## Appendix 1

### Using XML for eCTD Documents

It is recognized that XML is an open, non-proprietary way of describing information and that there are also an infinite number of ways in which XML can be used to describe document contents. In order to facilitate the use of XML as a format for Narrative, Structured and Graphical documents, standard means of describing contents should be used. For XML these means are defined through the use of a DTD or Schema, and therefore appropriate open, non-proprietary DTDs or Schemas should be specified for the format of XML-based documents.

The following is prepared as comment on the use of XML as a format for documents within the electronic Common Technical Document and specifically the use of the World Wide Web Consortium (W3C) Standard Scalable Vector Graphics (SVG) (and eXtensible Stylesheet Language Formatting Objects (XSL FO) for page delineation) as a format for Narrative, Structured and Graphical documents.

<b>Format Requirement</b>	<b>W3C Standard &amp; How the requirement is met</b>
<b>Shelf-life</b> Still usable in 50+ years	<b>SVG</b> As an XML format, SVG can be read by any text-browser (e.g. Notepad) and it is expected that text readers from one or more vendors will be available for the foreseeable future. SVG also integrally ties together presentation with content and so allows for documents to be created with exact representation (fidelity) at any point in the future.
<b>Vendor Independent</b> Not tied to a specific vendor	<b>SVG</b> As a W3C standard this is an open standard that is available to any organization with no charge and can have input provided into its development from any organization.
<b>Text-like</b> Clearly identify text flow, paragraphs, sections, tables etc. for copy/paste.	<b>SVG (&amp; XSL FO)</b> SVG can be used to represent text as well as vector and raster images, this text can be copied and pasted through the use of any appropriate viewer including free viewers listed on the W3C website. XSL FO can be used as a wrapper around SVG to specify the objects involved in the make up of a document, including sections, paragraphs, tables etc.
<b>Optimized</b> Uses minimum information to describe document contents.	<b>SVG</b> As a W3C XML Standard a collaborative effort to determine the most efficient way to represent information was determined.

<b>Easily Read</b> Can be read using off-the-shelf free/cheap products.	SVG SVG can be viewed using free viewers from Adobe and other organizations, these viewers are referenced on the W3C website ( <a href="http://www.w3.org/">http://www.w3.org/</a> ).
<b>Fonts</b> Support for different fonts & colors.	SVG SVG supports all IANA character sets and has RGB color representation for more than 16 million colors.
<b>Page Orientation, Size, Margins</b> Allow for different page orientations, paper sizes & margins.	SVG (& XSL FO) SVG is used to describe the contents of a page of information, this page can have any dimensions or other attributes, XSL FO can be used to associate different pages together with their orientation.
<b>Images</b> Allow the embedding of images within content.	SVG (& PNG) SVG is a standard that can be used for the display of 2-dimensional vector images and is fully integrated with the W3C Portable Network Graphics (PNG) XML standard for the display of raster images.
<b>Hypertext Linking</b> Allow hyper linking inter-/intra- document.	SVG (& X-Link/X-pointer) SVG is fully integrated with the W3C X-Link and X-Pointer XML standard for the provision of link information.
<b>Bookmarks</b> Allow references to specific content sections.	SVG (& X-Link/X-Pointer) SVG is fully integrated with the W3C X-Link and X-Pointer XML standard for the provision of anchor information.
<b>Page Numbering</b> Allow numbering of pages in the document.	SVG Page numbering is either an integrated part of the content (to maintain linkage between paper and electronic versions) or can also be controlled automatically through XSLT views of the SVG.
<b>Document Information</b> Allow additional information to be associated to the document.	SVG (& RDF) Any additional information can be included in the document through the use of W3C Resource Description Framework (RDF) XML Standard, this can be meta-data, audit trails or any other information.
<b>Indexing</b> Allow for full-text indexing and other search mechanisms within the content.	SVG As a text-based format this can be inherently full-text indexed, as a structured XML format additional information can be used to aid indexing including the use of categorization technology.

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