Guidance for Industry

M2: eCTD Specification

Questions & Answers and Change Requests

Companion Document: Current Q&As and Change Requests

(See Document Change History for version and date.)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
ICH

ICH

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

eCTD IWG Question and Answer and Specification Change Request Document

Version 1.14

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Document Change History

Version Number	Date	Description
Version 1.0	January 2003	Initial Baseline after reviewing questions submitted to ICH
Version 1.1	February 2003	ICH Steering Committee Meeting in Tokyo
Version 1.2	July 2003	ICH Steering Committee Meeting in Brussels
Version 1.3	July 2003	ICH Steering Committee Meeting in Brussels FDA Lawyer Comments
Version 1.4	July 2003	Following ICH Steering Committee Meeting in Brussels
Version 1.5	November 2003	ICH Steering Committee Meeting in Osaka
Version 1.6	January 2004	Following IFPMA notification of formating problems
Version 1.7	June 2004	ICH Steering Committee Meeting in Washington
Version 1.8	November 2004	ICH Steering Committee Meeting in Yokohama
Version 1.9	May 2005	ICH Steering Committee Meeting in Brussels
Version 1.10	November 2005	ICH Steering Committee Meeting in Chicago
Version 1.11	June 2006	ICH Steering Committee Meeting in Yokohama
Version 1.12	October 2006	ICH Steering Committee Meeting in Chicago
Version 1.13	May 2007	ICH Steering Committee Meeting in Brussels
Version 1.14	November 2007	ICH Steering Committee Meeting in Yokohama

Introduction

This question and answer document is a summary of questions reviewed by the eCTD Implementation Working Group (IWG) on the eCTD Specification. The questions answered here relate to common questions that relate to the eCTD in all three ICH regions. Many of the questions received on the Step 2 specification were addressed in Step 4 and do not appear in the list. Questions concerning the timeframe for implementation of region-specific application types, module 1 implementation, lifecycle management and those questions that relate to items in the specification that direct the reader to each region are answered in guidance documents published for each region.

Questions related to the table of contents for the Common Technical Document (CTD) should be directed to the CTD question and answer section of the ICH Website.

Some of the questions posed so far address change requests to the eCTD Specification. The change request section of this document addresses all those items received by the eCTD IWG and indicates their status.

This document will be updated as the specification undergoes change control or as new questions are submitted to the eCTD IWG.

Q&A No. 36 updated May 2007	
1	Ensure there is an ICH backbone file named index.xml in the sequence folder
2	Ensure ICH published checksum(s) of eCTD DTD is the same as checksum of eCTD DTD in 'util/dtd' folder
3	Ensure the index.xml is validated against the corresponding eCTD DTD version in the 'util/dtd' folder
4	Ensure the eCTD index.xml is validated for logical and correct attribute content as defined in the ICH eCTD specification as follows: - If the value of the operation attribute is new, then the modified-file attribute value is empty or not provided - If the value of the operation attribute is append, replace or delete, then the modified-file attribute will have a valid value - If the operation is new, append or replace, then the attribute xlink:href will have a valid value - Verify that the ID attribute value starts with a letter or underscore character
5	Ensure there is a xx-regional.xml[1] in the appropriate folder
6	Ensure regionally published checksum(s) of the DTD, Schema, and related files are the same as checksums of the corresponding files in the 'util/dtd' folder.
7	Ensure the regional index files are validated against the corresponding regional DTD, Schema, and related files (e.g., mod files) in the 'util/dtd' folder.
8	If using regionally required instance files (e.g., STF), ensure regionally published checksum(s) of the DTD, Schema, and related files are the same as checksums of the corresponding files in the 'util/dtd' folder.
9	If using regionally required instance files (e.g., STF), ensure the instance files are validated against the corresponding regional DTD, Schema, and related files in the 'util/dtd' folder.
10	Ensure the regional xml file (s) is validated for correct XML syntax and correct attribute content (consult regional guidance)
11	Ensure the checksum for every file is equal to the associated checksum stated in the relevant backbone (i.e., index.xml, xx-regional.xml)
12	Ensure all the files identified by an xlink:href reference exist. Regional authorities must be consulted as to whether the target of an xlink:href can exist outside the sequence in which the referencing leaf appears.
13	Ensure there are no unreferenced files in folders m1 through m5 (including subfolders other than 'util' subfolders)
14	Ensure the appropriate format is used for the modified file attribute in relation to the DTD being referenced. (Specification 3.0 vs. Specification 3.2)
15	Ensure that all file and folder naming conventions (length limits and allowable characters) comply with Appendix 6 of the eCTD Specification (Note: Folder and file names in the eCTD Specification are highly recommended, not mandatory (see Q&A No. 15))
16	Ensure that all the lowest level heading elements included in the submission contain at least one leaf
17	Ensure no PDF files are larger than 100 megabytes
18	Ensure that sequence numbers have 4 digits (i.e., numbers between 0000 and 9999)
19	Ensure that the sequence folder name matches the sequence number in xx-regional.xml (not applicable in Japan)
20	Ensure that leaf or node extension Title attribute is not empty. The only exception is a leaf element with the operation attribute value "delete" where the Title may be empty.
21	Ensure no files have file level security or password protection enabled
22	Ensure that the PDF Links and bookmarks are relative
23	Ensure that PDF files have been optimized for fast Web delivery

[1] Where xx represents the ICH region designator: eu for European Union; jp for Japan; us for United States regions

eCTD Specification Change Requests (received after the release of Step 4)

#	Requestor	M2 Sponsor	Specification Component	Description	Comments	Status	Action
00010	CTD-E FDA	FDA	m5-3-5	Multiple Indications	Resolved by CTD group, no implication for eCTD	Out of scope	
00020	Liquent	EFPIA FDA	4-62 (#371)	4-62 (#371) shows that DTDs and style sheets should be put in a dtd or style subfolder but on page 6-2 it shows that dtd files should be placed directly under util folder. Which is correct?	Appendix 4 is the definitive source of information, it should be made sure that it is corrected in the next version	Approved for specification change	Specification changed to Version 3.2
00030	EFPIA	EFPIA FDA	Page 4-8, Line 34	Incorrect use of hyphen	Must be changed	Approved for specification change	Specification changed to Version 3.2
00040	MHLW	MHLW	Page 2-5	Parta (UPPERCASE is not allowed) – not necessary to restrict to lower case	It is best to leave it as it is (lower case)	Rejected	
00041	MHLW	MHLW	Page 4-1	Full path of the File/Directory. Page 6-5 …Use the full path to refer to files. The full path is not shown in these examples.	Not relevant	Rejected	
00042	MHLW	MHLW	Page 6-5	Use the full path to refer to files. The full path is not shown in these examples.	Not relevant	Rejected	
00050	Liquent	FDA	3.2.A.3	Request 3.2.A.3 to be changed to a repeating element	Understood and will address in Q&A (No. 12) and then next version of DTD	Approved for specification change	Specification changed to Version 3.2
00060	FDA	FDA	Appendix 3, footnote 6	States that there will be as many subfolders as there are studies included. There may be some studies in Section 5.3 without patient data listings or CRFs.	Erroneous question, text in footnote is correct; question not relevant	Rejected	
00070	EFPIA	EFPIA FDA	ich-ectd-3-0.dtd	the element declaration <!ELEMENT m3-2-p-2-1-components-of-the-drug-product ((leaf |node-extension)?)> is different to all other element declarations: <!ELEMENT name ((leaf | node-extension)*)>	Element is no longer in the 8 October version of the dtd; not relevant any longer	Rejected	
00080	ECTD IWG	FDA	Header	Updated Version Number	Not relevant, version in header is correct	Rejected	
00090	EU	FDA	6-9 and 6-13 Table 6-8	Acrobat 5 is specified when it should read “PDF 1.3”	Change the examples (such as PDF 1.2 or PDF 1.3) in the specification to include both the ‘application version’ and the ‘file type’ version. Also, include some of this in Appendix 7	Approved for specification change	Specification changed to Version 3.2
00100	EFPIA EU	EFPIA EU	3.2.p.4	Structure of the DTD to support excipients is less than optimal	DTD will be updated, also addressed in Q&A No. 3	Approved for specification change	inform CTD Q; change next major release
00110	EFPIA EU	EFPIA EU	Appendix 3, 4	Clarify file names mandatory or optional. Inconsistent wording	Clarification is highly recommended; Q&A (No. 15) recommended before rewriting agreed that file names are optional	Approved for specification change	Specification changed to Version 3.2

00120	EFPIA EU	EFPIA EU	Appendix 4	Recommendation for the use of unique filenames where reviewers are likely to have several files open for comparison.	Unique file names as general principle will be recommended – related to Q&A of 110	Approved for Q&A	No. 15
00130	EFPIA EU	EFPIA EU	DTD – Appendix 6 Example	Use of the checksum; clarify use of checksum when delete operation is applied	Needs to be addressed in a Q&A (No. 21) Checksum should be Null	Approved for Q&A	No. 21
00140	EFPIA EU	EFPIA EU	Appendix 4, Section 3.2.S.2	Suggest **optional** use of sub folders to better structure documents	As all file and folder names are optional, this	Approved for Q&A	No. 17
00150	EFPIA	EFPIA	Appendix 4	States that the regional DTD and xml files have one naming convention, but the EU Module 1 has a different naming convention. Which takes precedence.	EU has been changed, not relevant any longer	Out of scope	
00160	EFPIA EU	EFPIA EU	Appendix 4 3.2.P.7	Suggest multiple files allowed for different container closure systems.	Flexibility over number of files to be included in revised M4 Organization document	Approved	M4 organisation document changed
00170	EFPIA	EFPIA	DTD	Use of "Title" attribute within structural elements of the DTD.	No "Title" attribute for the structure	Approved for specification change	consider structure representation and control as part of next major release
00180	JPMA	JPMA		Preliminary discussions on how to handle multiple indications	Duplication, see 00010	Out of scope	
00190	ECTD IWG		Cover Page	Add "International"	Needs to be changed	Approved	Cover page was changed
00200	Q&A		DTD	Make the indication attribute required	Change in DTD and specification necessary	Approved for specification change	Specification changed to Version 3.2
00210	Q&A		DTD	Need to consider how to update index.xml when there is an error in the backbone	Answer: should be consulted with regulatory agency	Approved for Q&A	No. 3
00220	Q&A	EFPIA		The specification be expanded to support two way communication		Out of scope	
00230	FDA	FDA	2-3 Checksum	Detailed explanation on using checksums when deleting a previously submitted file.	Not relevant as duplication to 00130	Rejected	
00240	FDA	FDA	Page 6-7	Make leaf ID required in eCTD Specification (at present is optional)	Change specification to make leaf ID required at leaf level	Approved for specification change	Specification changed to Version 3.2
00250	EFPIA	EFPIA		Zip files. A realistic mechanism to parcel up a small eCTD submission and attach to an email or simple FTP transmission is required. .zip is one simple option for the bundling together of the files within the directory structure required for an eCTD submission and hence being able to provide a single object to the agency in a highly efficient manner.	Zip is OS dependant, open standard archiving formats may be considered. Out of scope for IWG	Out of scope	
00260	EFPIA	EFPIA		Clarification should be given, with examples as to the intended content of the attribute 'application version'. The specification defines an attribute termed 'Application Version' but provides no examples of what might be used here. For example, is 'Acrobat v5 okay or should it be PDF v1.3. Other examples might relate to Word version when .rtf files are used reginally etc. It would be useful to understand the purpose of this attribute and hence what to use as valid terms.	Duplication, see 00090	Approved for specification change	Specification changed to Version 3.2

00270	EFPIA	EFPIA		Should bookmarks be presented expanded or collapsed? Should bookmarks for tables and figures be separate structures? Several options exist regarding the presentation of bookmarks. Firstly the bookmarks can be presented so that they are collapsed to the first level whereby the reviewer can expand those that they wish to explore or they can be presented fully expanded so that the review can see all the bookmarks but this may be a very long list in some documents. Secondly, the bookmarks can be presented sequentially, page by page, or they could be grouped with Tables and Figure appearing separately. Is there a preference form the agencies as to how they wish to see bookmarks presented.	Not sufficient experience yet for a firm answer across the regions. Suggestion that it is a company decision for the individual submission	Approved for Q&A	No. 18
00280	EFPIA	EFPIA		The specification should be developed to encompass a definition for acceptable digital signatures Several companies are wishing to move towards the use of digital signatures but there is no commonly defined acceptable standard and/or statement regarding signatures from ICH. ICH would be a sensible forum for such a standard to emerge. This should be taken on as a change control item but in the meantime some form of guidance through Q&A would be useful eg. what to do if you do have digital signatures – are they acceptable and what constitutes acceptability.	Appropriate for a short Q&A (No. 14) stating that there is no position on this point	Out of scope	
00290	EFPIA	EFPIA		The current upper limit of file size should be raised from 50MB. The original requirement for a maximum file size for pdf files of 50MB came from the initial FDA guidance document dating from 1998. Performance of networks and pcs has increased significantly from then. ICH should consider increasing the maximum file size to something larger. This will facilitate the preparation of documents – particularly legacy documents where scanning has been the only option.	Test whether file sizes of 100 and 75 MB can be accommodated by all regions Has been tested and can be accommodated in all regions	Approved for specification change	Specification changed to Version 3.2
00300	EFPIA	EFPIA		Clarification should be given, with examples as to the intended content of the attribute 'font library'. The specification defines an attribute termed 'font-library' but provides no examples of what might be used here. For example, is 'Arial' appropriate or would it need to be 'Arial, Arial Black, Arial Narrow, Arial Italic' etc. It would be useful to understand the purpose of this attribute and hence what to use as valid terms.	This it currently not used	Approved for Q&A	No. 19
00310	EFPIA	EFPIA		Can clarification be provided about the necessity to provide full text indices (eg. Adobe Catalogue files) and if desired by the agencies, how and where they should be included in the backbone.	There are no current plans to use Full Text Index in any of the regions. The section on providing pdf indexing requirements will be revisited in the next version of the	Approved for specification change	Specification changed to Version 3.2
00320	EFPIA	EFPIA		When an update occurs to a file, other documents may have redundant and inaccurate links to it. A mechanism should be established to manage either the redirection of this link and/or the highlighting that the link is pointing to a superceded document and the review tool(s) offers the updated document as an alternative	See change request form	Deferred	until more experience with lifecycle management of eCTDs
00330	EFPIA	EFPIA		The DTD should be modularised. For example, the leaf, so it can be used for other purposes such as in the regional module.	Harmonizing the technical approach to Module 1 with the other Modules of the eCTD is planned for the next major release	Approved for specification change	Specification changed to Version 3.2

00340	EFPIA	EFPIA		Additional operation attribute to be included in the spec to allow for the ref of a file from multiple places in the backbone but the mgmt of full attribute information only once. It is appropriate to make ref to the same file from many locations. In the eCTD the principle should be that the file is included only once but can be linked to from multiple locations in backbone. This is a good solution except when lifecycle means that this document is, e.g., replaced. Under this circumstance, each entry into backbone must be individually updated. The eCTD should include an option to provide a 'reference' operation attribute. For a new submission, primary location of a file would have the full metadata associated with it but at secondary locations, metadata could refer to the primary location in the backbone. Thus, when updating, it would only be necessary to update the operation attribute at the primary location, thus simplifying lifecycle maintenance and leading to the reduction of potential errors that would occur through updating only some of the links.	When the leaf ID will be mandatory (see 00240) this can be used to provide a reference to the primary entry in the backbone. Explanatory notes will need to be provided on how to utilize the leaf ID e.g. when multiple instances of a document are required.	Approved for specification change	Specification changed to Version 3.2
00350	EFPIA	EFPIA		Are .tiff files an acceptable format for provision with an eCTD submission or should they be converted to pdf? tiff is a commonly used format for scanned documents – particularly legacy documents and CRFs.	No, consult the section of the specification for acceptable formats	Approved for Q&A	No. 20
00360	EFPIA	EFPIA		The GxP requirements for signatures needs to be considered in the context of provision of multiple files for a study report – and in particular as it relates to an updated document. Under GCP and GLP signatures are required and in a paper process these cover the whole report. So in an initial submission the signature provided in a report can be taken to cover the whole report and is contemporaneous. However, once into the lifecycle management process electronically, it is possible to update only certain files eg. a new appendix. Guidance needs to be provided regarding the GxP interpretations of signature applicability – namely when do signatures also need to be updated and how should the process be designed to demonstrate exactly what each version of a signature actually applies to.	Has been taken to the CTD Coordination group November 2003	Out of scope	
00370	FDA/PhRMA	FDA	ich-stf-stylesheet-1-0a.xsl internal:vocabulary4leaf-labels-file-tag	Change <item>randomisations-scheme</item> to <item>randomisation-scheme</item> and <item>iec-erb-consent-form-list> to <item>iec-irb-consent-form-list</item> Use the singular form, randomisation, not the plural form of the word. Correct a probable error in the iec-irb-constent-form-list value.	Requestor asked to drop change request	Rejected	
00380	EFPIA	EFPIA	Appendix 4	Where optional granularity is allowed the specification only defines file names at the lowest level. Advice should be given regarding what file names to use at the higher level.	Reference is made in the Specification to the M4 granularity document	Approved for specification change	Specification changed to Version 3.2

00390	FDA/EFPIA	FDA/EFPIA	Page 2-1	Currently states that ICH Web has empty template. No template exists	Empty folder structure will be provided	Approved for Q&A	No. 13
00400	EFPIA	EFPIA	Appendix 9	The page numbering in Appendix 9 of the Specification is incorrect. It starts with 9-14 and should be 9-1.	Minor change, can be made at next edit.	Approved for specification change	Specification changed to Version 3.2
00410	FDA	FDA	Tracking Table	Close 00180 and delete text in first paragraph of description column	Requestor asked to drop change request	Rejected	
00420	Boehringer Ingelheim Pharmac. Inc.	FDA	Appendix 4: File Organization for the eCTD	We recommend that all sections of the eCTD Quality Module 3 be allowed the option of containing a single document, or multiple documents in each section and subsection. We agree that once a particular approach has been adopted (single or multiple documents), it should be maintained for the life of the dossier.	Single or multiple documents/files are already allowed in the eCTD. The eCTD Specification (appendix 4) needs to be updated and will be done at the next specification change	Approved for specification change	Specification changed to Version 3.2
00430	Boehringer Ingelheim Pharmaceuticals Inc	FDA	Appendix 4: File Organization for the eCTD	The "2.3 Introduction to the Quality Overall Summary" (Item 11 in the eCTD File Organization) is redundant to the "2.2 CTD Introduction" (Item 10 in the eCTD File Organization). We recommend that the "2.3 Introduction to the Quality Overall Summary" be deleted from the eCTD specification.	Not in scope of eCTD, as it is a content issue. Discussion with CTD Q confirmed that there is no need for change, as the placeholder is already there in the CTD Q document. If the numbering is corrected in the CTD Q document, the eCTD will make this change as well.	Rejected	
00440	FDA	FDA	DTD and Specification	Consider inclusion of Container/Closure system as an attribute		Deferred	until more experience with CTD
00450	FDA	FDA	Specification v3.0, pages 6-3 through 6-9 and 8-2	Ensure that approved change request #00240 is the currently accepted way all regions are using Leaf ID with the modified file attribute.	Change specification to make leaf ID required at leaf level	Approved for specification change	Specification changed to Version 3.2
00460	EFPIA	EFPIA	STF specification & M4 Granularity Annex	Is it feasible for legacy reports to continue to be submitted as a single file/document without the need for splitting up into separate files/documents as per the STF and the Granularity Annex. Is there a specific date from which al reports should be structured in the CTD defined way?	Mixed submissions (legacy as one file and reports written according to STF) are acceptable at the moment. A time frame for the transition will have to be defined	Approved for Q&A	No. 22
00470	EFPIA	EFPIA	Specification v3.0 & M4 Granularity Appendix	GLP and GCP inspectors expect to see consecutive page numbers across a report. CTD and eCTD allow page numbering by document/file. The two are incompatible.	Has been taken to the CTD Coordination group November 2003	Out of scope	
00480	JPMA	JPMA	Specification v3.0, Appendix 5	The listing of media types for eCTD submission is not necessary M2 recommendation on physical media and regional guidance should be referred to instead.	Correct at next specification change, section 5-2	Approved for specification change	Specification changed to Version 3.2
00490	JPMA	JPMA	Template Empty Folder Structure	Errors in template of empty folder structures	Update template folder structure	Approved	Empty Folder structure was updated Version 3.03
00500	JPMA	JPMA	Specification v3.0, Appendix 3	Errors in Appendix 3, Fig 3-3 and 3-4		Approved for specification change	Specification changed to Version 3.2
00510	JPMA	JPMA	Specification v3.0, Appendix 4	Inconsistency between line 23 and line 24 of Appendix 4 in the abbreviation of pharmacology	Correct line 24 to pharmacol	Approved for specification change	Specification changed to Version 3.2

00520	JPMA	JPMA	Specification v3.0, Appendix 2	The 256 maximum for length of path does not allow regulators to add to that path, if needed	Change page 2-4 the maximum length to 230 to allow regulators to add server names to the path (page 2-4)	Approved for specification change	Specification changed to Version 3.2
00530	ICH M2 IWG	ICH M2 IWG	Specification v3.0, Table 6-3	Clarify the operation attributes REPLACE and APPEND	Correct specification	Approved for specification change	Specification changed to Version 3.2
00540	EFPIA	EFPIA	Specification v3.2	For a submission that has been filed utilising v3.0, is it possible t move to v3.2? Comment from vendors: "Some sponsors have already sent submissions using 3.0 and but may not realize that they have to stick with 3.0 for the rest of that applications life cycle as introduction of ID's and use of ID's in modified file attribute won't allow sponsors to change over to 3.2". Is this true and if so, what is recommended by the agencies? It does not seem practical to stay with an old version forever. Can this situation b rectified and how can it be avoided in future when the specification is updated again?	The recommendation is that the ID is mandatory, even if using 3.0, to avoid compatibility problems; For previously submitted files, consult with the Regulatory Agency to ascertain how to resolve the lifecycle issue.	Approved for Q&A	No. 26
550	EFPIA	EFPIA	Specification v3.2	Clarification should be provided regarding any restrictions to character sets in the id value. According to the W3C definition an ID attribute value uses the "name" definition and must start with either a letter, an underscore or a colon and then can be followed by any combination of letters (upper or lower case), digits, period, hyphen underscore or colon. FDA has recently returned a pilot eCTD submission to J&J because the ID attribute value contained an underscore character. They stated that the syntax for the ID attribute must match the syntax of the file name (as specified in the ICH eCTD spec this means lower case letters digits and hyphens only). They said the ICH spec stated this syntax for the ID attribute quoting page 2-4 and 2-5 of the version 3.2 spec as the basis for this statement. They also said the ID could not contain an underscore as it was being used in hyperlinks, and may be disguised by the formatting of the linking text (if it uses an underline).These two specs are not compatible. Clarification should be provided.	FDA agrees that underscores can appear in the leaf id, as long as it is not the first character	Rejected	

560	EFPIA	EFPIA	Specification v3.2	Clarification should be provided by all ICH regions as to whether node extensions can be used in Modules 2-5 The ICH spec allows node extensions to be used in Modules 2-5 and their use in Module 1 is a regional matter. FDA states that node extensions are not supported in any part of the submission and this therefore invalidates the ICH spec. Experience on production of submissions for Europe demonstrates that node extensions are required to deliver a navigable structure for Modules 4 and 5. At present this means that eCTDs are not re-usable across regions and thus will create significant amounts of rework for industry. FDA should accept node extensions in Modules 2-5.	FDA has concerns that node extensions might be over-used. Experience during the testing phase has confirmed the validity of these concerns. In many instances, the requirement for STF in the US eliminates the need for node extensions. There may be some occasions where the use of node extensions could be justified, and that should be discussed with FDA on a case by case basis. For the time being, other regions are able to accept appropriate use of node extensions in	Approved for Q&A	No. 28
570	EFPIA	EFPIA	Stylesheet	The ICH standard stylesheet does not adequately support the use of node extensions – the display is corrupted. The ICH spec supports the use of node extensions at the lowest level. When node extensions are used, the stylesheet does not display the title of the file correctly. All files under that node extension are included in the title for each file. The attached screenshots demonstrate the issue. Slide 1: xml source code Slide 2: display in style sheet. Text in yellow box should be m5351 (plus node extension detail, ideally) Slide 3: As displayed in the latest version of The DataFarm viewer(attached PPT slides)		Approved	Stylesheet was rewritten
580	EFPIA	EFPIA	Specification v3.2	There are significant incompatibilities between the output of certain eCTD builder and viewer tools because of differences of interpretation of the spec and differing items being validated. ICH should develop a validation suite. Recent experience within Europe (and US) has highlighted that the 'valid' output of one vendor product is not necessarily valid as input to another. This is leading to the need to test and correct submissions before filing. The incompatibilities are arising because one product is expecting certain items to be addressed in particular ways (although a specific way is not stated in the eCTD spec). This has led to incompatible interpretations. This could be avoided if a suite were to be developed by ICH which could be used by all tools.	The issue has been recognised. 1st step is to define the criteria that the various vendors use for validation.	Approved for Q&A	No. 36
590	Datafarm Inc.	PhRMA	Specification v3.2	Is the file name for an individual file fixed from beginning to end of life cycle?	Answer in the negative	Approved for Q&A	No. 23

600	Datafarm Inc.	PhRMA	Specification v3.2	Regional XML reference in INDEX.XML According to DTD and spec all documents submitted within the submission should have a reference (leaf) within the XML backbone. When amendments, variations, etc. are sent the appropriate Operation and modified file attributes should be used to maintain the life cycle of that document. Does this rule apply to the leaf that refers to regional XML file? Please note even though the actual document is controlled by the regional authorities the reference and life cycle management of this leaf/document lies within the ICH DTD.		Approved for Q&A	No. 24
610	Datafarm Inc.	PhRMA	Specification v3.2	Application Form and Cover Letter Life Cycle… According to DTD and spec all documents submitted within the submission should have a reference (leaf) within the XML backbone. When amendments, variations, etc. were sent the appropriate Operation and modified file attributes should be used to maintain the life cycle of that document. Does this rule apply to the leaf that refers to Application Form and Cover Letter that exists in all sequences? Also, this is something that is common across regions.Please note even though the actual document is controlled by the regional authorities it will be nice to have a common set of guidelines as they are common across regions.	Refers to specific regional documents within Module 1. Consult regional guidance.	Out of scope	
620	Datafarm Inc.	PhRMA	Specification v3.2	Text file with MD5 Value and cover letter… The MD5 value for index.xml in a Text file is clearly specified in the spec. Still it led to some confusion with interpretation. Please clarify: 1. There is only one index-md5.txt with index.xml md5 value stored within that file per sequence and it stays along with index.xml. 2. There is no need for index-md5.txt for regional xml file as this MD5 value is already present in the index.xml 3. It is impossible to generate the MD5 value and place that value in the cover letter (page 5-2). This will change the MD5 value of the cover letter, regional xml and index.xml. May be this can be placed on the Media Label.	In appendix 5, the eCTD Specification requires a paper cover letter that is also to be submitted as a pdf (cover.pdf) not linked to the backbone. This is the cover letter to which the md5 text is to be added as an appendix. These matters are also dealt with in regional guidance.	Approved for specification change	Next minor release

630	Datafarm Inc.	PhRMA	Specification v3.2	The ID value requirement is not clear and requires additional specifications. Per ICH specifications on page 6-8 it states…"Unique identifier for this file in the XML instance. Leaf ID must start with a character." It will be nice if this clearly states that ID value should: -Start with alpha character -Only alpha and numeric values are allowed and no symbols or special characters -No spaces are allowed -Length of the ID value should not exceed "n" characters Regional review systems have their own limitations in terms of length of the leaf attribute values such as title. It will be nice if ICH controls these just like they are controlling href maximum length and file name maximum length.	With the exception of the requirement that the id must start with an alpha character, there are no limitations on the contents of these fields, subject to technical limitations.	Rejected	
640	GSK	EFPIA	Specification v3.2	There is an inconsistency in the description of the maximum file size Appendix 7: Specification for Submission Formats of the eCTD, page 7-1: the guidance states: "To ensure that PDF files can be accessed efficiently, PDF files should be no larger than 100 megabytes." However, on page 7-4 of the eCTD Specification, under Page Numbering, the guidance states "Two exceptions to this rule can occur (see details in the guidance for the modules of the CTD. First, where a document is split because of its size (e.g., >50MB), the second or subsequent file should be numbered consecutively to that of the first or preceding file."For consistency, the latter occurrence should be updated to 100MB.	This is a typographical error in the specification. The maximum file size is 100 MB, not the 50 MB given in the example.	Approved for specification change	Next minor release
650	Centocor BV	EFPIA	Specification v3.2, Appendix 4, file organization for Module 3.2.S	File organisation to support manufacturer should be consistent across Modules 2.3.S, 2.3.P, 3.2.S and 3.2.P. At present 3.2.S. is subdivided per substance/manufacturer, 3.2.P has only subdivision by product while 2.3.S and 2.3.P have no subdivisions. Can subdivisions for manufacturer in all sections be defined? See also change request 660	For Modules 2.3.S and 2.3.P it is already possible to differentiate by manufacturer, by the file name & by attributes. For Module 3.2.P, refer to CTD Q how they see the organisation of 3.2.P	Rejected	Refer second part to CTD Q
660	Centocor BV	EFPIA	Specification v3.2	File organisation for 3.2.P should follow the same principles as for 3.2.S. with respect to differentiation between manufacturers. 3.2.S has a folder organisation by substance/manufacturer, 3.2.P has no such organisation below product. A folder structure should be introduced for each manufacturer.	Refer to CTD Q to determine how they want the organisation of 3.2.P and its subsections.	Out of scope	Refer to CTD Q

670	Centocor BV	EFPIA	Specification v3.2	To prevent maintenance of identical copies of documents, it should be possible to make a link to the appropriate document elsewhere in the same submission or any of the previous submission in the eCTD life cycle.Examples are given in the original change request. This could be achieved if an additional operation attribute (e.g. "link") is allowed, next to new, append, replace, delete.	A file should only be included once within a single sequence. The requirements for references to one file across sequences are different in each region. The eCTD EWG will address the "link" concept as it relates to	Approved for Q&A	No. 38
680	Aventis	JPMA	ICH eCTD Style Sheet	ICH eCTD Style sheet cannot work for “Node-Extension” xml-instance		Approved	Stylesheet was rewritten
690	GSK	EFPIA	Specification v3.2	Moving to a new version of a specification during the lifecycle of a product. Do you expect that we would stay with a given DTD version for the duration of an application, so that as long as we are submitting to the same application we would use the same DTD version as used for the original submission, or would we be expected to apply new versions of the DTD within a certain time period, across all submissions regardless of whether they are new or ongoing? Also, if there is a need to change DTDs, how will the agency viewing tools present the cumulative view if there is a structural change to the submission eg. renaming of old sections, introduction of new sections etc.		Approved for Q&A	No. 27
700	Lorenz	EFPIA	Specification v3.2	Can an eCTD be submitted that covers more than one region? If the content of Modules 2-5 in a submission is to be the same between two or more regions is it allowable to submit more than one Module 1 in the same eCTD?		Approved for Q&A	No. 29
710	Lorenz	EFPIA	Specification v3.2	Are vendor specific style sheet allowed? Style sheets may include function to redirect reference links to other files.		Approved for Q&A	No. 30
720	Lorenz	EFPIA	Specification v3.2	Is an MD5 value required for the regional index file Are regional MD5 checksum files (##-regional-md5.txt) mandatory, optional or not allowed?		Approved for Q&A	No. 31
730	Lorenz	EFPIA	Specification v3.2	Japanese characters are two bytes. Can 64 characters still be used for file/folder names in Japanese?		Approved for Q&A	No. 32
740	Lorenz	EFPIA	Specification v3.2	Clarification of the allowable leading character of the ‘id’ attribute. Table 6.8 of the specification defines that the id value should start with a character. This is perhaps imprecise since a characte could be alpha, numeric, or other. Numeric is not allowable according to W3C definitions. Could a more precise definition be provided as to what are actually allowable characters?	see Q&A No. 11	Rejected	
750	Lorenz	EFPIA	Specification v3.2	What length of ‘title’ attribute is allowable/recommended? The Title field appears to have no restriction to the number of characters. Since the titles of documents such as study reports can often be several hundred characters, could guidance be given whether there is actually any restriction and whether a full title is of value to the reviewer or whether a shortened form should be used?	~~Propose up to 1024 bytes with recommendations to keep titles concise~~. Make recommendation around use of concise title length (changed from previous comment (see above) during June 2006 meeting)	Approved for specification change	Next minor version
760	Lorenz	EFPIA	Specification v3.2	Do submission sequence numbers have to be consecutive eg. 0005 always has to be submitted after 0004 or are there circum-stances where 0005 can be submitted before 0004?		Approved for Q&A	No. 33
770	AstraZeneca	PhRMA	Specification v3.2 See page 6-11, “Instructions for Submitting Sections as Paper.”	Please can you clarify whether the contents of the Application-Version field, reference the PDF version or the Acrobat Version (e.g. PDF Version 1.4, or Acrobat 5)?	We have already addressed this as a change request (#00090) where our response is that it should be the PDF version. It looks like some Acrobat version numbers are still given. We'll need to correct that properly at the next edition.	Approved for specification change	Next minor version

780	AstraZeneca	PhRMA	Specification v3.2 See "Methods for Creating PDF Documents and Images."	Scanning Standards - is it possible to scan at 600 dpi, instead of the ICH recommended 300 dpi? Kanji documents look unclear when scanned at 300 dpi.	Specification should be changed to 'at least 300 dpi'.	Approved for specification change	Next minor version
790	AstraZeneca	PhRMA	Specification v3.2 See "Instructions for an Amendment, Supplement, or Variation."	Standardisation of PDF Global Acrobat Specifications - What plans are there to standardise the PDF Global Acrobat Specifications for eCTD (e.g. Distiller settings)? What are the PDF settings upon distilling the PDF: what version (1.3?), is the PDF optimised? Does the PDF have thumbnails?	The PDF section of the eCTD specification addresses standardization across all regions; use of PDF or XML will be evaluated for next specification.	Rejected	
800	AstraZeneca	PhRMA	Specification v3.2 See page 6-11	Placebo and Comparators - in applications for clinical trials, where should the CMC information on Placebo and Comparators be located? For example, treat each placebo and each comparator as separate 3.2 Drug Products within the application OR include both placebo and comparator information under 3.2 Regional?"	This is a CTD Q question, it will be handed over to the CTD Q group.	Rejected	
810	EFPIA	EFPIA	Q&A 28	Could the eCTD IWG please review this Q&A in the light of experience in Europe? As part of the Q&A the following statement has been made "For the time being, other regions are able to accept appropriate use o node extensions in compliance with the eCTD specification (i.e. their use is discouraged unless there is no other feasible means to submit the information). The IWG will review this situation." Experience in Europe is that routinely the node extension is bein used, typically at the lowest level to differentiate between studies and so organize the files per study. Other examples are used higher up the backbone, wherever some differentiation is required that is not supported by attributes. No problems appear to be occurring and it would make sense to review this guidance since actually the use of node extensions is 'expected' in Europe	Q&A No. 28 has been supplemented.	Approved	
820	GSK Canada	FDA	Specification v3.2 and regional specifications	In a subsequent submission, can the operation attribute 'new' be used against a document at a specific position in the backbone where there has already been a document in the previous submission? The vendor of a an eCTD builder product has interpreted the spec that at no point in the lifecycle of the eCTD can there be submission of a document with the same name/title included where the operation attribute is assigned as new in the subsequent submission. An example would be where a variation/amendment contains a 'cover letter'. This is always related to the specific filing. 'New' is the attribute that should be used. 'Replace' or' delete' are not relevant and 'append' is not appropriate to use since it is not necessary to refer to the previou as there may be no relationship intended. There are other examples where this issue can arise within Modules 2-5, for example in Module 2 where a QOS may be totally new and not rely upon 'append' nor require 'delete' or 'replace'. Could clarification on the acceptability of the use of 'new' in subsequent submissions?		Approved for Q&A	No. 34
830	Liquent	PhRMA	Each Region's implementation guidance	Willingness of regions to accept eCTD-only Which countries will accept eCTD only as official submission of archive? And under what conditions? Are there any non-ICH countries you are aware of that would be willing to take an eCTD?	Regional authorities have communication on these questions - please refer to those.	Rejected	
840	Liquent	PhRMA	Specification v3.2	Versions of PDF files Will there be a mandate regarding the different versions of Acrobat documents to be accepted and/or expectations of backwards compatibility, while acknowledging that are only recent versions that may be purchased? The latest Guidance document on the FDA site indicates PDF 1.4, and while Acrobat Distiller may be set to create lower version PDFs, once manipulated in a later version of Acrobat (which is often necessary to add hyperlinks, bookmarks, etc.), the file retains tha later version and cannot be 'saved down'.	see answer to Change request 00790	Rejected	

850	Liquent	PhRMA	Specification v3.2	At the DIA EDM Conference someone asked about hyperlinks and submission lifecycles. For documents that the sponsor knows will be updated at a later date (e.g. as part of the 120-day safety update), the FDA said it was fine to not provide hyperlinks in the initial application; rather, you should provide a physical citation so that the reviewer can get there via the backbone. Is that approach acceptable in all regions?	This is a business related question, which cannot be answered by the eCTD IWG. Consult regional authorities on a case by case basis.	Rejected	
860	Liquent	PhRMA	Specification v3.2	Can you provide any best practice recommendations around using the append operation; is there an expectation that the content being appended will include contextual clues as to the portion of the original document to which it applies?	This is a business related question, which cannot be answered by the eCTD IWG. Consult regional authorities on a case by case basis.	Rejected	
870	Liquent	PhRMA	EU Regional specifications	With the issuance of v1.0 of the EU application form in XML, is there a timeframe when it will be accepted and/or mandated? Can you provide details as to how it and supportive files should be included in an eCTD (supportive files with the application form XML file or in the main util directory, etc.)?	EU regional question	Rejected	
880	Liquent	PhRMA	EU Notice to Applicants	Has any further discussion occurred regarding the handling of eCTD lifecycles in Mutual Recognition Procedures? It has been suggested that eCTD lifecycles may be 'branched' to help support multiple submissions to different concerned member states. Will further guidance clarify this soon?	EU regional question	Rejected	
890	Liquent	PhRMA	Specification v3.2	Can you provide further clarification on the related sequence element? Should it only contain references to sequences which are included in modified-file paths, or any sequence to which information being newly submitted may pertain?		Approved for Q&A	No. 35
900	Liquent	PhRMA		What is the training and education plan for agencies in Europe to aid them in understanding the implications of the lifecycle opportunities and challenges of eCTD?		Rejected	
910	Liquent	PhRMA	Specification v3.2	Are there any recommendations regarding the length of a document and the need for it to have its own internal table of contents? Are bookmarks representative of the document structure an acceptable substitute to a table of contents?	Refer to page 7-3 of the Specification 3.2.	Rejected	
920	Liquent	PhRMA	US and EU Regional specifications	With the SPL and PIM initiatives, are there plans to issue specifi guidance as to how to include these documents and their supportive files in an eCTD as well as address the lifecycle considerations?	Refer to regional guidances on Module 1	Rejected	
930	Liquent	PhRMA	eCTD DTD	Is it expected that the ID attribute for non-leaf elements will be used and are there lifecycle implications to using it?	An example would be helpful to understand this question.	Rejected	
940	Liquent	PhRMA	Specification v3.2	Is there a (technical or practical) limit to the number of character used for the leaf ID? Would a GUID be considered appropriate for this value?	Reference to W3C documents Qname	Approved for specification change	Next minor version
950	Liquent	PhRMA	Specification v3.2	If a document is appended multiple times – sequence 0001, 0002, and 0003 all contain a leaf with an operation="append" and modify a leaf submitted in 0000, is there a point at which thi becomes unwieldy from a review perspective? Is there an expectation that at some point, it makes more sense to replace the file submitted in 0000 with the sum-total that comprises the current document as a single leaf and delete the appended leaf elements?	This is a business related question, which cannot be answered by the eCTD IWG.	Rejected	
960	Liquent	PhRMA	eCTD DTD and Written Specification	How are the link-text and xref elements expected to be used in the eCTD? So far, we have not found application for them and would like to know where they apply.	Reserved for future use - clarify in spec	Approved for specification change	Next minor version
970	Liquent	PhRMA	Specification v3.2 and regional specifications	The November 2004 Q&A includes questions regarding the use of node-extensions (#28, Change Request 00560) and we understand from our customers that node-extensions are necessary in the EU, but they are specifically discouraged in the v3.2 Specification. Has further thought been given regarding the expectation of their continued use?	Duplicate change request, see 00810	Rejected	

980	Liquent	PhRMA	Specification v3.2	Are there any plans to update the ICH and/or regional Paper CTD specification(s) to further facilitate parallel submission of eCTD and paper while paper is still required in some regions (as in the EMEA v0.3 guidance document*Practical guidance for the paper submission of regulatory information in support of a marketing authorisation application when using the Electronic Common Technical Document ("eCTD") as the source submission* from June 2004)?	Refer to regional guidances	Out of scope	
990	Liquent	PhRMA	Specification v3.2	Are there other sections of the eCTD in Modules 2-5 or any region's Module 1 that are being considered for XML/structured content as opposed to PDF?	For structured XML files refer to regional guidance. For use of XML in place of PDF refer to change request No. 00709	Out of scope	
1000	Liquent	PhRMA	Specification v3.2	Has any further discussion occurred to address the lifecycle linking issues of preventing stale links without requiring the resubmission of content?	see change request 003	Deferred	
1010	Liquent	PhRMA	The eCTD Backbone File Specification for Study Tagging Files v2.6, November 2004	The v2.6 STF specification does not mention content-blocks, but they are still in the DTD; is there an expectation that these will b used, and if so, can examples be provided?	Refer to US regional guidance	Out of scope	
1020	Liquent	PhRMA		There is a zip file for v2.6 of STF on the ICH site, but the FDA site still has v1.1. Assuming the 2.6 version is the correct version to be used, if using the cumulative approach, and given how the format of the xlink:href changed from a folder/file path to the indirect reference of the backbone, and the change to the usage intent of the property element, if I have previously submitted STFs according to the 1.1 specification, should the new STF remove the property elements from the old doc-content elements and update the format of the xlink:href attributes? If the Accumulative approach is taken, do previously submitted STFs need to be replaced to reflect the current usage?	Refer to US regional guidance	Out of scope	
1030	Liquent	PhRMA	eCTD DTD	Are there any plans to use the leaf attributes of role, actuate, and/or show, or to remove them from the specification if they are not planned to be used?	Reserved for future use - clarify in spec	Approved for specification change	Next minor version
1040	Liquent	PhRMA	Guidance for Industry – Submitting Marketing Applications According to ICH-CTD Format	Is there an expectation that companies will continue to submit hybrids (eNDA/eBLA with CTD content) for a specific timeframe? Is there an expectation that any hybrid requirements will eventually be included in eCTD? Can FDA tell us how many hybrids they've received vs. eCTD this year and last?		Out of scope	
1050	Liquent	PhRMA	US Module 1 v1.1 March 2004	Can you provide further clarification on the related sequence element? Should it only contain references to sequences which are included in modified-file paths, or any sequence to which information being newly submitted may pertain?	Duplicate change request, see 00890	Rejected	
1060	PhRMA	PhRMA	eCTD DTD, STF DTD and CTD granularity	Similar to M 3, granularity of information in M 4+5 should be clearly defined and accepted by all regions. There should be no regional differences in acceptability based on granularity; when same info is provided across regions, granularity (and any defined attributing or file-tagging or keywording) must be same. File-tags, keywords and attributes should be treated as ICH controlled vocabularies to ensure that same content file is attributed the same way across regions. Explanations defining application + use of each term is needed to support consistent interpretation, understanding and use. **Manifestations** There is currently an ICH file-tag called "nonclinical-study-report". Recent FDA implementation of the STF document indicates not to use this ICH-approved term and to use the "US" term, "nonclinical-data". Regional changes to ICH file-tags should be approved by ICH and reflected in ICH documentation. There should be no need for "info-type" tags as all tags should be ICH-approved.	FDA will draft a modification to their current STF specification and share it with the M2 EWG for comment. Once all comments are addressed, FDA will publish a new STF specification.	Out of scope	Regional Issue

1070	FDA	FDA	eCTD message	The current eCTD implementation does not enforce consistency, promote automation or promote reuse of data (e.g., excipient – can not be searched across submissions because it is a free text field). Modeling techniques may allow us to more easily identify areas for collaboration or data sharing. To do this we think a move to a schema approach is necessary for clear identification of data and relationships. In addition, a more agile specification (e.g., controlled vocabular outside of backbone; ability to reuse the same transport mechanism for different product types) would allow us to extend the specification to other product lines (i.e., reuse of spec).		Approved for specification change	Next major release
1080	PhRMA	PhRMA	Specification 3.2	Specification needs to be updated to show how to use message to support following scenarios consistently in all 3 regions (related to cc 320): reuse of same physical file 1) within same submission instance without duplicating file (multiple references from single backbone); 2) content across different submission instances of single Application without duplicating file (references from different backbone instances within single marketing application); 3) content across different submission instances of multiple Applications (references from different instances of different marketing applications); The solution has to address cases where: a) appropriate operation attribute value necessary to indicate that file has been submitted (and perhaps reviewed) in another context; b) subsequent file lifecycle changes (e.g., delete, append, replace have occurred and apply to all re-use contexts; c) subsequent file lifecycle changes have occurred and are not applicable to all contexts.	Unclear whether this can be handled through documentation (more careful language in the specification or a parallel "Implementation Guide") or whether it necessitates a technical change to the DTD. **Options:** After careful analysis of needs: 1) Clarify (with examples) how to achieve above within specification. 2) Create Implementation Guide that specifies recommended mechanism and includes examples. 3) Modify existing technical DTD and then perform steps 1 or	Approved for Q&A	No. 37 No. 38
1090	PhRMA	PhRMA	eCTD DTD, STF DTD and CTD granularity	**Concepts of a Logical Document** - provides an organizational construct for documents comprised of more than one file (e.g., within any eCTD element, there is no consistent mechanism to identify which files are related and contribute to "the document" as a whole; especially significant when there is more than one document in that element) - provides an organizational construct to create\maintain relationships between files comprising a document over time (lifecycle management of a document) - provides an organizational construct to provide a static representation of a document in the backbone allowing updates to "the document" without changing the referential target in the backbone - when you need to reuse the logical document you could provide the reference to the logical document rather than the collective set of files that form the logical document		Approved for specification change	Next major release

1100	PhRMA	PhRMA	eCTD DTD and STF DTD	Current implementation policy of allowing individual regions to determine whether or not to accept aspects of the specification potentially creates a divergence in specification implementation. This may lead to one region rejecting an application while another one accepts it. While regions may have “preferences” in receipt of info, these ‘preferences” should not override the specification. **Examples** 1.The exact same collection of files compiled\organized using STF or using node extensions would not be acceptable to all regions even though both approaches are approved by ICH. 2. Use of either Accumulative or Cumulative Approach for STF management is not acceptable in all regions. **Possible Solutions** Option #1: Remove different approaches and agree on a single approach. Option #2: Require all regions to accept any valid submission utilizing the specification as written.	A subgroup will be testing changes that involve moving all study tags to the eCTD DTD to incorporate STF functionality to the eCD backbone. This testing will also ensure that the eCTD backbone will continue to support approaches in other regions to submitting study content. M2 members may communicate this issue to vendors.	Assigned to a subgroup for testing	
1110	EU/EFPIA	EU/EFPIA	Specification v3.2	EU Delegation would like to reopen Change Request #220 regarding two way communication. In eCTD, a significant amount of data in the lifecycle is created by agency and sent to applicant. This includes lists of questions, documentation of decisions, lists of post approval commitments, etc. EU Delegation also sees this issue linked to tracking of approval status (see separate Change Request) where notification of approval or rejection comes from the agency. eCTD specification should be modified to incorporate this exchange of information. This request is a matter of some urgency as EU is currently implementing PIM standard for exchange of labelling information. This standard includes two way exchange of data and the plan is to incorporate this in EU M 1 spec. Under the current spec this necessitates finding a workaround for the agency to industry communication.	At the moment it is a regional requirement. EU solution within module 1 may be feasible as an interim solution.	Deferred	Consider for the scope of the next major release
1120	EU/EFPIA	EU/EFPIA	Specification v3.2	EU Delegation proposes addition of a means to track “approval status” of the groups of sequences associated with an activity to change authorisation. One of the uses of this information is to allow consumers of the eCTD to view an “approved” view of the lifecycle that specifically excludes data that is under review, rejected or withdrawn from consideration. Proposal is related to concept of two way communication raised in a separate Change Request. Approval status is another example of information sent from the agency to applicant. Solution could be made at a regional level but EU Delegation believes that other regions could benefit from this information and a solution at ICH level would be advantageous.	At the moment it is a regional requirement. EU solution within module 1 may be feasible as an interim solution	Deferred	Consider for the scope of the next major release
1130	EU	EU	Specification v3.2	Experience has shown that 'valid' output of one vendor product is not necessarily valid as input to another. This mandates to test and correct sub-missions before filing and leads to incompatibi-lities with tools installed in agencies. This arises because one product is expecting certain items to be addressed in particular ways (although a specific way is not stated in the eCTD spec). This has led to incompatible interpretations. eCTD spec should be improved to allow for specific technical validation criteria to be incorporated permitting consistent implementation across tool and regions. Use of Schema to optimize automated validation of eCTDs is anticipated. This change request relates technical validation criteria related to eCTD spec, not scientific and regulatory content of files/documents. We also note that use of XML Schema may not address all possible technical validation criteria (e.g. file size of leaf files) and other solutions may be required.	Earlier provided information as Q&A 36 based on Change Request 580 (submitted 2004-05-28) is considered not sufficient. M2 to take action and arrange for a special Session at the DIA Annual meeting or FDA could host a meeting around the DIA Annual meeting Also considered for ICH 7/DIA meeting in 2007	Approved for specification change	Next major release

1140	Health Canada	Health Canada	Specification 3.2	The spec and DTD need to support manage-ment of submission throughout lifecycle of a product. Common processes across all regions must be supported in a harmonized approach. This includes: 1. initial submission 2. subsequent submission as response to a request from the agency 3. subsequent submission initiated by the applicant There is a need to be able to support/track parallel review of subsequent submissions. Current specs are intended for a linear increment in submission sequences. Some of the current operation attributes are still causing confusion in tool vendors an agency guidance, e.g. sequ 0000 myfile.pdf new sequ 0001 myfile.pdf append sequ 0000 sequ 0002 myfile.pdf replace sequ 0001 What should be the current view? How is this resolved? There are several similar examples of combination of operation attribut that will cause an error message in the viewing tool or confusion for the reviewer.	Provide more clarity on the use of append Changes may be shared with others by members of the IWG	Assigned to a subgroup for testing	PhRMA taking the lead on minor modifications to the eCTD spec and bring results to the next meeting
1150	Health Canada	Health Canada	Specification v3.2	Current spec defines message from industry to agency. The initia intent of the spec was to support two way communications. This section was never documented. A message from agency to industry needs to be defined. Can be linked to life cycle management.	Duplication, see 1110	Deferred	Consider for the scope of the next major release
1160	JPMA	JPMA	Leaf File	Linking between files should be discouraged because it is imposible to maintain the linkage if the documents will be revised.		Out of scope	Refer to EWG for next major release
1170	JPMA	JPMA	PDF File	Acrobat version was updated. The specification states Acrobat Reader 4.0. The suppported version of PDF should be explicitly stated. This should be considered carefully, including consideration of Japanese Acrobat, as there are bugs that affect viewing some PDF versions in some Reader versions.	Use specific pdf version rather than Acrobat version number in specification document. Before next minor release, Q&A No. 40 has been issued	Approved for specification change	Next minor release
1180	JPMA	JPMA	STF	Please reconsider the handling with Study Report Information in STF. Creation of STF files are additional work.	A subgroup is working to resolve this issue together with the issue in change request 1100	Assigned to a subgroup for testing	
1190	JPMA	JPMA	Specification 3.2	Any future eCTD specification should be backward compatible with the current eCTD specification. If the ICH M2 is planning to revise the eCTD spec, we would like to continue to use the current eCTD data, especially eCTD backbone XML instance. Furthermore, it is likely that many companies and regulators hav invested in systems based on the current eCTD spec. If the next major eCTD spe will be released, these systems will have to be modified. Modifications should be minimized. We need compatibility between current and new eCTD system or at least we need a way to easily convert eCTD from the current standard to the new one.	This question is covered in the Change Control Process for the eCTD	Rejected	
1200	JPMA	JPMA	Specification 3.2 and style sheet	The current DTD has a fixed TOC. TOC of browser is showed based on style sheet information. In Japan, we would like to have a Japanese TOC to accelerate the review and facilitate communication between Agency and Applicant. Furthermore, the fixed eCTD TOC name is different from actual CTD TOC name.		Out of scope	Refer to EWG
1210	JPMA	JPMA	Specification 3.2	In the future, there is a possibility that the CTD structure (TOC) will be revised. This will require a corresponding eCTD specification change. Frequent changes to the eCTD specificatio will be difficult and a burden on industry, regulators and vendors If M2 plans to revise the eCTD specification, it should consider easy maintenance of the eCTD specification in the case of CTD TOC revisions.		Out of scope	Refer to EWG

1220	JPMA	JPMA	Specification 3.2	Nobody can predict what CTD structure changes will occur in the future. Therefore, the eCTD specification should be designed to accommodate CTD changes. The eCTD specification should use XML Namespace to permit inclusion of other XML messages (e.g. include the ICSR message in eCTD).		Out of scope	Refer to EWG
1230	JPMA	JPMA	Specification 3.2	The current eCTD style sheet has fixed tags. Then it is impossible to adapt to some CTD TOC requirements (e.g. it is impossible to show the manufacture and ingredient in 2.3 TOC which is the CTD requirement). The eCTD specification should have some flexibility to show the requirement and CTD specification intentions.		Out of scope	Refer to EWG
1240	MHLW	MHLW	Instance	According to fitting for current evaluation process, it will be required not only full XML instance but also cumulative XML instance.	Need to address as business need in Japan	Out of scope	Refer to EWG
1250	MHLW	MHLW	Leaf File	For the reuse the documents, it should be allow to use XML documents as for leaf file.		Approved for Q&A	No. 39
1260	DOCUMENTUM	PhRMA	STF Stylesheet (ich-stf-stylesheet-2-2.xsl), Version 2.6, 2004-11-17	The original stylesheet will not handle xlink:href value correctly. It assumes that the href value would contain a sequence number. [This is not the case from FDA sample files.] The following will locate the file with the original style sheet (but still have problems in displaying the STF page properly because does not handle relative path correctly): <doc-content xlink:href="../../../../../../../0000/index.xml#e5155"> Rewriting the above in an equivalent way: <doc-content xlink:href="../../../../../../index.xml#e5155"> causes the following message: Document title = **The XML page cannot be displayed** We fixed the above issue and other problems such that STF can be displayed properly. In addition, to allow sequence numbers to be absent, we also allow a submission name to be of any length, not just 4 chars (e.g. "0000").	eCTD IWG will post a new stylesheet as soon as possible	Approved	Stylesheet was rewritten
1270	PhRMA	PhRMA	STF specification Version 2.6, 2004-11-17	Every example of a leaf that references a STF file is using the attribute "version" field incorrectly. The “version” attribute is for the Sponsor’s internal version number or version identification for the file referenced by the leaf. Should the information cited under “version” in the text of the STF specification actually be cited under "application-version"? Or is “application-version” only to be used for content files (e.g., PDF, MSWord)?	ICH is investigating this error. This will be updated in the next minor release.	Approved	Next minor release
1280	PhRMA	PhRMA	Specification v3.2	In many instances, sponsors need to establish an ‘append’ relationship between leafs in a single submission message and the current spec advises not to do this. Business Cases: 1) Large files may need to be split. Regulators and sponsors prefer that these files be related in the message (via ‘append’) rather than each being submitted as ‘new’ with no relationship. 2) A previously unsubmitted granular document is to be submitted. There are clear ‘append’ relationships in the leafs of this collection (e.g., amendments to protocol). In providing this collection, sponsors wish to establish leaf relationships to be consistent in the presentation of this type of information (compared to other documents of this type) and to support more efficient lifecycle management in future. It is a clearer message construct to show the relationships than to just submit them all as “new”.	1) Append should not be used to relate split files as cited in Specification v3.2, page 6-3 2) Approved for inclusion in next minor release	1) Rejected 2) Approved for inclusion in next minor release	Reviewed Oct-2007

1290	Acusphere	FDA	Specification v3.2 Page 4-25, and eCTD IWG Q&A and Specification Change Request Document Version 1.9, change request 00050 and Q&A No. 12.	We request clarification on the folder and file naming convention for the numerical portion of Section 3.2.A.3. eCTD defines that for each novel excipient a separate folder should be created in section 3.2.A.3., with each folder uniquely identified through the use of the excipient's name (e.g. 32a3-excip-name1 and 32a3-excip-name2). The directory/file structure is to follow that of the drug substance section in Module 3. Could guidance be given on the naming conventions for the numerical portion of the subfolders and files within Appendix 3.2.A.3, when taking into account that the appendices for the novel excipients follow the drug substance structure, but that these excipients are not the drug substance? (e.g. For the section entitled "3.2.S.2 Manufacture", our approach would be to omit the "s" in the novel excipient folder name and use one of the following conventions: 32a32-manuf-Name1 or 32a3-2-manuf-Name1). Is this approach acceptable?	Issue will be addressed during the requirement's gathering period for the next major release of the eCTD specification	~~Approved for specification change~~ (updated Oct-2007) Deferred	Refer to CTD-Q (updated Oct-2007)
1300	Acusphere	FDA	Specification v3.2 , Pages 4-19 and 4-20, and eCTD IWG Question & Answer and Specification Change Request Document Version 1.9, Q&A No. 3.	We request clarification on the amount of information about a drug's novel excipients that is necessary to include in Section 3.2.P.4 when the information is included in Section 3.2.A.3. CTD defines that for each noncompendial excipient a separate section 3.2.P.4.1 through 3.2.P.4.4 can be provided, and that 3.2.P.4.5 and 3.2.P.4.6 are separate files. The way to structure these elements in the eCTD was addressed in the eCTD IWG Question & Answer and Specification Change Request Document Version 1.9, Q&A No. 3. Should a folder encompassing files 3.2.P.4.1 through 3.2.P.4.4 be repeated for novel, noncompendial excipients, even though CTD has specified that novel excipients should be discussed in sections 3.2.P.4.6 and 3.2.A.3? Also, can clarification be provided around how much information about the novel excipients is required in 3.2.P.4.6 if more detailed information is provided in Section 3.2.A.3? Would it be sufficient to simply refer reviewers to 3.2.A.3 for more information?	This is primarily a CTD question and should be addressed to the ICH secretariate.	Out of scope	
1310	GE Healthcare	EFPIA	M4 Granularity Appendix	The Granularity document states "Additionally, all pages of a document should include a unique header or footer that briefly identifies its subject matter. In a paper-based drug submission, a similar identifier should be used on a tab that precedes the document, to facilitate finding that document within the dossier. An abbreviation of the full section number and title can be used." With the eCTD there is a significant amount of metadata available to the reviewer to allow easy identification of the document concerned without the necessity to place an identifier in the header or footer.		Approved for Q&A	No. 41
1320	ING America Inc.	JPMA	eCTD Version 3.2 specification and current published eCTD Q&A - Version 1.11 June 8, 2006	There is confusing guidance regarding location of CRFs, appears to conflict with EU and US regional guidance (problem area in ETICS). Current confusion to be eliminated. Treatment in CTD and eCTD is different. **For eCTD:** PDF files for CRFs and indiv. pat. data listings should be organised by study in folder for M5.3.7. Yet, in index.xml file, leaf elements for CRFs and indiv. pat. data listings should be included under same heading as other study report files with addit. information included with any accompanying study taggin file. Also, a repeat of leaf element can be placed under heading 5.3.7 CRFs and Indiv. Pat. Data Listings. Datasets, if required by region, should be organised according to regional guidance. Files for public. and lit. refs should be located in folder for M5.4 Yet, in index.xml file leaf elements for public. and lit. refs should be included under same heading as other study report files with additional information included with any accompanying STF. In addition, a repeat of leaf element should be placed under heading for 5.4 Lit. Refs.	Q&A # 25 has been replaced with Q&A #42 to address this issue	Approved for Q&A	No. 42

1330	ING America Inc.	JPMA	eCTD Version 3.2 specification, and various related specifications for STF, and regional modules.	The ICH M2 eCTD Q&A 36 item numbers 2 and 6 state that an eCTD submission utilise correct and accurate DTDs and schema and that the MD5 checksum of each DTD or schema must match the “published” MD5 checksum. However, only one of the numerous DTDs (and schema) – the eCTD V3.2 DTD - is published in a fixed web location together with its checksum. This has caused confusion on the part of tool vendors, sponsors and agencies. During the ETICS study, several different versions of the EU V1.1 DTD were in use by vendors. Other modified DTDs were also found. Recommenation: all DTDs and schemas, ICH or regional, related to the eCTD be published on the ESTRI web site, together with their respective MD5 checksums and any required stylesheets or related files (e.g. valid-values.xml). Each region should commit to maintaining current information on the ESTRI web site through an agreed upon process (perhaps a review and confirmation of these items at each M2 meeting).	Each region is responsible for publishing checksums for DTDs and Schemas created and used in their own region. Checksums for ICH DTDs will be available on the ESTRI website.	approved	update the ESTRI website to add the STF DTD checksum
1340	ING America Inc.	JPMA	STF Specification Version 2.6 with STF V2.2 DTD – 2004-11-17	The “content-block” element and its sub-elements remain in the DTD, but the usage of content block has been removed from the specification and it is not intended to be used. It should be removed from the DTD also for consistency and accuracy.	Agreed, should be updated in next release of the STF specification and DTD	approved for specification change	next minor release
1350	WSMI	EFPIA	DTD	The link in the header "http://www.ich.org/ectd" leads to an error message.Suggestion is to replace it with "http://estri.ich.org/ectd" The reference for XLINK is not actual “http://www.w3c.org/1999/xlink” Suggestion is to replace with “http://www.w3.org/TR/xlink”	Agreed, should be updated in next release of the ICH eCTD specification and DTD	approved for specification change	next minor release
1360	eCTDconsultancy BV	EFPIA	No changes but clarification -- eCTD specs v3.2 Appendix 6	Please, confirm that a single file can replace multiple files from various previous sequences.	No, a single leaf operation can only target a single leaf element. It is important to distinguish between leaf elements and files. eCTD specifications describe the management of leaf elements, not files.	approved for Q&A	no. 43
1370	eCTDconsultancy BV	EFPIA	No changes but clarification -- eCTD specs v3.2 Appendix 6	Please, confirm that a single file in an eCTD lifecycle can be replaced multiple times	No, once a leaf element has been replaced in an application it is no longer current. Only the current leaf can be replaced in a subsequent sequence.	approved for Q&A	no. 44
1380	eCTDconsultancy BV	EFPIA	eCTD specs v3.2 Appendix 4 Row 90	Please, revise guidance to have a single 3.2.P.4.1 file for each excipient, irrespective whether it concerns compendial or non-compendial excipient.	Please refer to the ICH M4 granularity annex which indicates that 3.2.P.4.1 may contain one or more documents. The eCTD guidance provides the flexibility to have each excipient (compendial or non-compendial) in a separate file.	Out of scope	refer to CTD-Q
1390	eCTDconsultancy BV	EFPIA	eCTD specs v3.2 Appendix 4 Row 90	Please, allow references be made to multiple regional pharmacopoeia in one and the same document. Compendial excipients are excipients that are described in one or more compendia. If excipients are described in multiple compendia, is it allowed to list all relevant compendia and not limited to the compendium relevant for a single country? This allows maximum reusability of the documents 3.2.P.4.1. The same principle is true for the references to pharmacopoeia in documents like 3.2.S.4.1 and 3.2.P.5.1.	This is out of scope of M2 IWG	Out of scope	refer to CTD Q

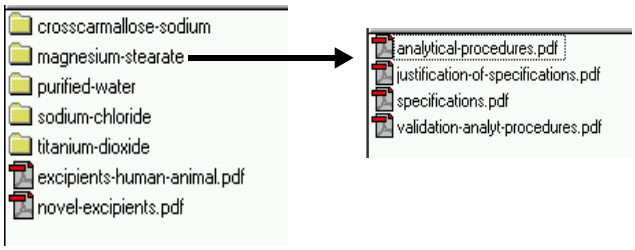
1400	eCTDconsultancy BV	EFPIA	eCTD specs v3.2 Appendix 4 Row 90	How to update the eCTD metadata if the name of an excipient changes, as indicated in e.g. the USP/NF or European Pharmacopoeia? The names of excipients have to be incorporated in the metadata of an eCTD. It is even reflected in the folder names under 3.2.P.4. During the lifecycle of a medicinal product the name of a particular excipient used may change over time without alterations being made to the formulation. How to deal on the level of the eCTD with alterations in the name of a particular compendial excipient? How to deal on the level of the eCTD with alterations in the name of a particular noncompendial excipient?	The eCTD specification does not have an explicit mechanism for changes to attributes during life cycle. As a work around, applicants would delete all leafs within the element with the incorrect excipient attribute and re-submit them within an element with the corrected excipient attribute. This work around would apply to both compendial and non-compendial excipients. Please consult your agency before performing this operation.	approved for Q&A	no. 45
1410	eCTDconsultancy BV	EFPIA	eCTD specs v3.2 Appendix 4	How to deal on the level of the eCTD with an excipient that was non-compendial during the first submission and has become compendial during at a later stage? Compendial excipients should not clustered in one document 3.2.P.4.1. When an originally non-compendial excipient gets described in pharmacopoeia, the applicant can provide a replacement 3.2.P.4.1 with the operation replace and having 3.2.P.4.1, 3.2.P.4.2, 3.2.P.4.3 and 3.2.P.4.4 as modified files This question/suggestion is related to Question 3 on granularity of documents for compendial excipients and Question 1 on replacing multiple files with one replacement file.	This is out of scope of M2 IWG	Out of scope	refer to CTD-Q
1420	eCTDconsultancy BV	EFPIA	eCTD specs v3.2 Appendix 4	Please, provide guidance that the manufacturing site is to be mentioned for the attributes “Manufacturer” for Drug Substance and Drug Product The names of manufacturers have to be incorporated in the metadata of an eCTD. It is even reflected in the folder names under 3.2.S and 3.2.P. During the lifecycle of a medicinal product the name of manufacturer may change withou alterations being made to the production processes. If submitted as paper, such a change was considered an administrative one. However, when the manufacturing name has been used, it has a huge impact on the structure of the eCTD lifecycle, resulting in a fragmented current and cumulative view of the eCTD lifecycle. If the manufacturing location (city) is used, a name change has no impact on the current and cumulative view of the eCTD When the city is used in the metadata and a manufacturers moves its plant to another location, it would result in a new 3.2.S or 3.2.P anyhow and the change will be visible as intended.	The eCTD specification does not have an explicit mechanism for changes to attributes during life cycle. Details of the manufacturer attribute needs to be referred to CTD-Q. Mechanism to change manufacturer will be analysed in release 4.0.	deferred	refer to CTD-Q
1430	eCTDconsultancy BV	EFPIA	eCTD specs v3.2 Appendix 4	Please, provide guidance that the manufacturing site “common” can be used for those documents that are independent of the manufacturing site involved in the production process of Drug Substance and Drug Product The following sections in Module 3 are independent of the manufacturing plant: • 3.2.S.1 General Information • 3.2.S.3 Characterization • 3.2.P.1 General Description and Composition • 3.2.P.2 Pharmaceutical Development • 3.2.P.3.1 Manufacturers If these documents have to be listed under each manufacturer, a document might be incorporated in the folder structure onece, but in the eCTD it has to be linked multiple times. As a result, the lifecycle on the leaf level has to be repeated multiple times. The use of “common” as value for the attribute “manufacturer” will eliminate this redundancy.	Not currently defined by the specifications.	deferred	refer to CTD-Q

1440	eCTDconsultancy BV	EFPIA	eCTD specs v3.2 Appendix 4	Please, provide guidance that the attribute “product-name” does not concern the trademark, but the distinction between the active component and diluent component in case of a powder and solvent for solution for injection. Moreover, for INDs, it can be used to describe the comparator drug or placebo formulation.	Not currently defined by the specifications.	deferred	refer to CTD-Q
1450	AstraZeneca	EFPIA	ICH eCTD Q&A 40	ICH eCTD Question Number 40 asks whether it is acceptable to submit PDF V1.4 files across all regions. Although the answer given is in the affirmative, it actually goes much further than mere ‘acceptability’ by appearing to make V1.4 mandatory for eCTDs. Shouldn’t V1.4 be ‘acceptable’ or perhaps ‘preferred’ (if justified) rather than ‘mandatory’?	Q&A 40 is being retired and Q&A 46 is created to read: all regions have agreed to accept PDF 1.4. Please consult regional guidance to submit other versions of PDF.	Approved for Q&A	Q&A #46
1460	Mission3	PhARMA	eCTD V3.2 specification, Page 2-2	Mission3 submits this change request with the suggestion of migrating the narrative content of submissions from PDF to XML. An XML model that fits the needs of this industry will yield significant benefits to both sponsors and regulatory reviewers.	The M2 EWG continues to monitor document format standards. The M2 EWG cannot recommend the general	deferred	deferred to SENTRI WG
1470	Roche Products Ltd	EFPIA	ICH Q&A, Q&A36, item 12	ICH Q&A36, item 12 says “Ensure all the files identified by an xlink:href reference exist”. This should be clarified to state where the files can exist.	Regional authorities must be consulted as to whether the target of an xlink:href can exist outside the sequence in which the referencing leaf appears. This text will be added to Q&A #36 item 12	approved	Q&A #36 revised
1480	Roche Products Ltd	EFPIA	ICH Q&A36, Item 20	ICH Q&A36, item 20 states “Ensure that leaf or node extension Title attribute is not empty (except when the operation attribute i delete)”. It is not clear why the parenthetical condition for delete is in place.	The item 20 statement is revised to read: Ensure that leaf or node extension Title attribute is not empty. The only exception is a leaf element with the operation attribute value "delete" where the Title may be empty.	approved	Q&A #36 revised
1490	Roche Products Ltd	EFPIA	DTD	The approved Change Request 00050 says that the element for Module 3.2.A.3 will be made a repeating attribute in Version 3.2 of the specification. This does not appear to have been done.	agreed, cardinality will be changed from ? to *	Approved for specification change	next minor release
1500	Take Solutions Ltd	EFPIA	Specification v3.2 and/or Q&A document	Differentiation of more than one novel excipient in Module 3.2.A.3	agreed, add excipient attribute in the DTD	approved for specification change	next minor release
1510	PhRMA	PhRMA	ich-stf-stylesheet-2-2.xsl	The ICH STF Stylesheet currently posted gives inconsistent display results in Internet Explorer. It seems to work in some cases but not in others. STF files which were viewable with the older version of the stylesheet are no longer always viewable.	STF stylesheet version 2.2 is being analysed.	approved	fixing in progress
1520	PhRMA	PhRMA	Valid-values.xml	There are differences in the values listed in the valid-values file posted on the ESTRI website and the valid-values file posted on the FDA website.	Applicants are advised to follow regional guidance. The ICH list will be analysed and corrective action will be taken in the future	approved	next minor release of STF
1530	EXTEDO – IABG Life Sciences Solutions	EU	DTD only	Optionally solving the conceptual weakness of generating broken links or the need of resubmitting documents only in order to update hyperlink information.	ICH M2 acknowledges the receipt of the proposal and will consider it with the business requirements for eCTD next major release.	deferred	next major release

1540	PhRMA	PhRMA	DTD & Written specification, Appendix 4 (including comment text), 6 and 8	The eCTD attributes for manufacturer should be removed from the DTD and written specification for 2.3.S, 2.3.P, 3.2.S, 3.2.P	out of scope	deferred	refer to CTD-Q
1550	PhRMA	PhRMA	Written specification, Appendix 4, all line items for module 3 filenames	All Filenames for Module 2.3 and Module 3 in appendix 4 should appear in italics - to indicate they are optional, and not mandatory	further analysis of the specification to be done	approved	next minor release
1560	PhRMA	PhRMA	DTD, Written Specification	Section 3.2.P.8.3 should be made a repeatable element with optional attributes of strength, package configuration, storage condition and manufacturer. Suggest a minimum of two of the four are required if technically possible.	out of scope	deferred	refer to CTD-Q
1570	PhRMA	PhRMA	Written Specification, Appendix 4 and 6. comment and example text.	Comment text (examples in App 4 and 6) suggest drug product strength as an extension of the dosage form attribute “name of dosage form through inclusion of strength should be provided ie. tablet-5mg” We suggest removing all references to drug product strength in the eCTD attribute for dosage form where the drug product is described.	out of scope	deferred	refer to CTD-Q
1580	PhRMA	PhRMA	eCTD specification ver 3.2 appendix 7	Is PDF/A-1 an acceptable PDF file format for documentt submitted in a eCTD?	PDF/A-1 is an archive format and does not meet the ICH review requirements for use with an eCTD. Requirements for archive format across regions will be identified and emerging technology will continuously be monitored to identify suitable archive formats.	Approved for Q&A	Q&A #47
1590	Datafarm inc.	PhRMA	Specification v3.2 and/or Q&A document	During the last ETICS study it was clear the storage of physical CRF files was not consistent. Datafarm followed the ICH rule based on Q&A #25. When that answer was withdrawn we looked for regional guidance. We currently place the leaf under the appropriate CTD element for the study and the physical file is stored under 5.3.7 folder within a study folder. Question: FDA: Where should we place CRF files? EU/HC: Where should we place CRF files? Do you want all CRFs in 5.3.7 or under the section where the study documents are presented? JP: Where should we place CRF files? Do you want all CRFs in 5.3.7 or under the section where the study documents are presented? All: Can we expect updated specifications/guidelines from the ICH or regional agencies prior to or along with v3.3.3?	This question is already addressed in Q&A 42	Out of scope	
1600	eCTDconsultancy Ltd	EFPIA	M2 eCTD stylesheet	Change the M2 eCTD stylesheet so that: 1.Sections are presented as the logical CTD structure, rather than formatted according to the underlying XML 2.It is possible to show when one document has been pointed to by multiple leafs in a single sequence. A benefit of presenting in this way would be that if the guidance changed and included advice to vendors on the viewing and processing of metadata, thi way of processing/viewing across a lifecycle would solve the problem currently associated with replacing structural metadata.	There are multiple ways to display data through a stylesheet; a common view is supported via the current stylesheet. ICH has no plans to modify the currently accepted stylesheet.	Rejected	

1610	PhRMA	PhRMA	eCTD specification ver 3.2 Heading Element 3.2.A.3	Current change request #1290 suggests an update to ICH M4Q to accommodate a proposed folder structure for data content in 3.2.A.3 Novel Excipients, similar to that presented in 3.2.S but no additional definition is provided. Heading Element 3.2.A.3 requires a sub-folder structure simila to that for 3.2.S Drug Substance. Current M4Q guidance states data should be provided 'similar to that included for 3.2.S' To maximize reviewability of data presented for a novel excipient, it is advised that additional subelements be introduced to the eCTD XML backbone to provide content organization similar to that described for 3.2.S. To avoid confusion with other similarly named heading elements, it is recommended that a new sub-section be named as 3.2.A.3.1 OR formally treat novel excipients as drug substances under 3.2.S and provide a standard for distinguishing the active ingredient from the novel excipients.	This has been addressed previously in CR #1290 and deferred for future consideration.	Deferred	Refer to CTD-Q
1620	PhRMA	PhRMA	The written specification, appendix 4	1) In order to support a more consistent implementation of the eCTD Specification in all countries, all optional filenames and folder names should be represented in italics. Currently there is a mix in the document and individual Health Authorities are interpreting the Specification to extreme degrees (e.g. Belgium). 2) The highly recommended, yet optional, filenames in the Specification should be shortened. 3) The eCTD folder names should also be shortened or made optional to help reduce path length.	All ICH-defined file and folder names within the m2-m5 folders are optional. Highly recommended names for directories and files are provided in Appendix 4 of the specification. Where file and folder names are presented in italics applicants will substitute these with file names in accordance with their own naming convention. Also refer to Q&A 15 and eCTD Specification version 3.2, pages 2-1, 2-5 and 4-1.	rejected	
1630	PhRMA	PhRMA	eCTD v3.2	The full utility of the eCTD standard is limited by the inability to accurately generate current views of an application which distinguish 'current, approved' from 'current, submitted'. Tool vendors should be encouraged to develop a mechanism which allows sponsors to control the display of submitted information to distinguish a 'current, submitted' view of post marketing changes to a dossier from a 'current, approved' view of changes.	This is an addition to requirements to support life cycle management. These requirements will be considered in the next major release of the eCTD specifications.	Deferred	next major release
1640	PhRMA	PhRMA	ICH M2 specification Appendix 3, Appendix 4, and Appendix 8 3.2.A.1	In Appendix 3, General Considerations under Module 3 Quality, in Table 3-3 change the Description for 3.2.A.1 from "Facilities and Equipment (name, manufacturer)" to "Facilities and Equipment (Name, Manufacturer, Facility)". In Appendix 4 File Organization, change Item 123's Title from "Facilities and Equipment (name, manufacturer)" to "Facilities and Equipment (Name, Manufacturer, Facility)" In Appendix 8 XML eCTD DTD: allow for a new repeatable element 3.2.A.1.Facilities and Equipment (Name, Manufacturer, Facility)	Referred to CTD-Q.	Deferred	Refer to CTD-Q
1650	PhRMA	PhRMA	ICH M2 specification Appendix 4 Item 39	Review the progress of standards development around use of harmonized terminology or controlled vocabulary for 'drug substance name' in M5: Data Elements and Standards for Drug Dictionaries as it may relate to a harmonized approach to this Module 3 eCTD attribute.	Deferred until a standard terminology is defined	Deferred	
1660	PhRMA	PhRMA	ICH M2 specification Appendix 4 Item 39	Regarding the use of the mandatory eCTD attribute, drug substance name, indicated by 'substance-1' in the ICH M2 guidance, the comment under Item 39 of Appendix 4 for the CMC attribute called 'substance-1' could be softened to allow either the current option or the option to utilize a [shorter] internal company code or specify that the attribute and the folder name do not need to be exactly the same in order to reduce path lengths.	The wording under Item 39 of Appendix 4 will be revised.	Approved for specification change	Next minor release

1670	EFPIA	EFPIA	eCTD Specification, version 3.2, page 2-3, page 5-2 and the eCTD DTD.	The requirement to create and manage the MD5 checksum for each and every leaf with content in the eCTD is a major burden on any creator of an eCTD. It is acknowledged that the creation and management of a single MD5 is, in itself, not particularly burdensome. However, the creation of even only a small numbe quickly becomes troublesome. A checksum is defined in Wikipedia in this way "A checksum is form of redundancy check, a simple way to protect the integrity of data by detecting errors in data that are sent through space (telecommunications) or time (storage). It works by adding up the basic components of a message, typically the asserted bits, and storing the resulting value. Anyone can later perform the same operation on the data, compare the result to the authentic checksum, and (assuming that the sums match) conclude that the message was probably not corrupted." The checksums included in an eCTD are not being used in this way. An invalid checksum should indicate a corruption and should lead to the non-processing of the submission. However, typical usage sees only a flag raised but processing continue. The checksum in the eCTD might usefully be a single checksum	To be discussed as part of requirements gathering for next major release.	Deferred	Consider for next major release
1680	FDA	FDA	eCTD Specification, version 3.2, page 2-5, Appendix 3.	The current eCTD specification prescribes specific folder names to be used when publishing eCTD submissions. In addition, the current specification calls for a maximum path length of 230 characters to enable regulators to add additional characters. Experience has shown that submitters attempting to utilise the prescribed naming conventions will frequently exceed the 230 character limit aften resulting in the loss of integrity of the path a they are processed by the operating system. This change proposes to modify the recommendations on folder naming and reduce the maximum recommended path length.	To be discussed as part of requirements gathering for next major release.	Deferred	Consider for next major release

Question	Answer	Approval Date
A paper CTD may contain more than one copy of the same document. In the eCTD, do you have to include more than one copy of a file?	Separate entries in the XML backbone for each reference of the file can accommodate this need. The file should be included once in an appropriate place in the folder structure. Avoid duplicating the file.	February 2003
How should cross-references be presented in the eCTD?	CTD cross-references can be supported in the eCTD through the use of hyperlinks.	February 2003
Is it possible to change the values previously assigned to XML node attributes (e.g., the case where no value or the wrong value is placed in indication and later it is decided that a value/different value is necessary)?	Currently no. This question generated change requests 00200 and 00210.	February 2003
It is very difficult to work out how to construct a valid index.xml file for the Control of Excipients section of Module 3 (3.2.P.4) without having to duplicate entries in the backbone and without deviating from the intended CTD structure. CTD expects that for each excipient a separate section 3.2.P.4.1 through 3.2.P.4.4 can be provided and that 3.2.P.4.5 and 3.2.P.4.6 are separate files. The eCTD cannot deliver a structure in which entries for 3.2.P.4.5 and 3.2.P.4.6 are not repeated either in the folder structure or as entries in the backbone. This question was generated by change request 00100.	One way to construct a backbone is as follows: Repeat the element m3-2-p-4-control-of-excipients for each excipient and assign the excipient attribute (e.g., magnesium stearate, and purified water) for each repeat. Under each of these include the leaf elements covering documents for 3.2.P.4.1, 3.2.P.4.2, 3.2.P.4.3 & 3.2.P.4.4. It is not necessary to include the leaf elements for 3.2.P.4.5 & 3.2.P.4.6 here. Then create another repeat of the element m3-2-p-4-control-of-excipients and assign the excipient attribute value 'animal-human-novel'. Include the leaf elements for 3.2.P.4.5 & 3.2.P.4.6 here. The directory/file structure may look something like this :  whilst the structure of the index.xml file would be like the image on the next page:	February 2003


```
<?xml version="1.0" ?>
<!DOCTYPE ectd:ectd (View Source for full doctype...)>
- <ectd:ectd xmlns:ectd="http://www.ich.org/ectd" xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="3.00">
  - <m3-quality>
    - <m3-2-body-of-data>
      - <m3-2-p-drug-product>
        - <m3-2-p-4-control-of-excipients excipient="crosscamallose-sodium">
          + <m3-2-p-4-1-specifications>
          + <m3-2-p-4-2-analytical-procedures>
          + <m3-2-p-4-3-validation-of-analytical-procedures>
          + <m3-2-p-4-4-justification-of-specifications>
          </m3-2-p-4-control-of-excipients>
        - <m3-2-p-4-control-of-excipients excipient="magnesium-stearate">
          + <m3-2-p-4-1-specifications>
          + <m3-2-p-4-2-analytical-procedures>
          + <m3-2-p-4-3-validation-of-analytical-procedures>
          + <m3-2-p-4-4-justification-of-specifications>
          </m3-2-p-4-control-of-excipients>
        - <m3-2-p-4-control-of-excipients excipient="purified-water">
          + <m3-2-p-4-1-specifications>
          + <m3-2-p-4-2-analytical-procedures>
          + <m3-2-p-4-3-validation-of-analytical-procedures>
          + <m3-2-p-4-4-justification-of-specifications>
          </m3-2-p-4-control-of-excipients>
        - <m3-2-p-4-control-of-excipients excipient="sodium-chloride">
          + <m3-2-p-4-1-specifications>
          + <m3-2-p-4-2-analytical-procedures>
          + <m3-2-p-4-3-validation-of-analytical-procedures>
          + <m3-2-p-4-4-justification-of-specifications>
          </m3-2-p-4-control-of-excipients>
        - <m3-2-p-4-control-of-excipients excipient="titanium-dioxide">
          + <m3-2-p-4-1-specifications>
          + <m3-2-p-4-2-analytical-procedures>
          + <m3-2-p-4-3-validation-of-analytical-procedures>
          + <m3-2-p-4-4-justification-of-specifications>
          </m3-2-p-4-control-of-excipients>
        - <m3-2-p-4-control-of-excipients excipient="animal-human-novel">
          + <m3-2-p-4-5-excipients-of-human-or-animal-origin>
```

Certain TOC tags are not required by the DTD. 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.	To be consistent with CTD general Q&A, always include these attributes as appropriate: - substance - manufacturer - product-name - excipient - indication - dosage form	February 2003
Appendix 4 provides specific folder names for some sections and states other sections can typically be submitted, as individual files. What is the definition of 'typically' and what should be done when they are not typical?	There are now clear definitions of what is recommended for the granularity of documents provided in the ICH guidance on 'Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use'. This describes what is considered to be the appropriate granularity for each section of the CTD and hence eCTD. Where there is no definition provided in the organisation document, applicants are free to construct the dossier as they see fit so long as it adheres to the conventions for folder and file naming described in the eCTD specification.	February 2003
Is there any control in the eCTD Specification over terminology to be used for indications?	No	February 2003
How will the reviewer view and use the “append” operation attribute? It would also be useful to have clarifications on how review tools within agencies will handle these attributes.	The eCTD Specification is concerned with the transport of electronic CTDs from applicant to regulator. Consult regulatory authorities in each region on the electronic review tools each use to view this format.	February 2003
Will questions from Health Authorities be provided electronically using the specification?	The eCTD Specification provides a transport mechanism for one-way traffic from applicant to agency. This question generated change request 00220	February 2003

It is recommended to have the name of the root folder to be the application number or registration number of the drug. Unfortunately, in some European countries companies don't get the application number prior to the submission. In the case of an MRP each country will give a different number creating an issue for naming the root folder. In some countries, the application number is given per pack size and/or strength, and the unique application number will be difficult to identify. A unique identifier such as for the FDA submission is therefore quite difficult to achieve in Europe.	Contact the regulatory authority for guidance.	February 2003
For the ID attribute, is it allowable to utilize an internal applicant identifier or would it need to be more understandable in order to support reasonable human identification (e.g. in reviewer to applicant correspondence about an issue).	The ID attribute is intended to be a unique reference within the submission that can be used to reference the item from another item within the XML document. XML requires the ID to begin with an alphabetic character. If an internal ID generator uses only numbers, appending a number to a leading alphabetic character that then could be used as the ID can create the ID.	February 2003
The eCTD Specification allows for one novel excipient in 3.2.A.3. What happens if there is more than one? This question is identified in change request 00050.	The regulatory authority should be consulted for a solution until the change request is resolved.	February 2003
The specification currently states that there is an eCTD empty folder template on the ICH website. One is not located there. Where is it? This question was generated by change request 00390	A file which can be downloaded and run to create an empty eCTD folder template is now available on the ICH website.	July 2003
What is the position on the use of digital signatures within the eCTD? This question was generated by change request 00280	Currently there are no plans for the M2 Expert Working Group to address this issue. Regional guidance should be consulted for the current use of digital signatures.	July 2003

Are the filenames for documents referred to in Appendix 4 of the specification mandatory or optional? This question was generated by change request 00110 and 00120	Filenames in the eCTD are optional. The ones provided are highly recommended. To assist the reviewer when several similar files are open at the same time, it can be appropriate to consider alternative naming conventions that could provide unique, understandable filenames. The general provisions for naming of files are in Appendix 6 of the Specification.	July 2003
Can clarification be provided about the necessity to provide full text indices (eg. Adobe Catalogue files) and if desired by the agencies, how and where they should be included in the backbone? This question was generated by change request 00310	Full text indices are not required by any of the ICH regional agencies and therefore the provision of guidance is not necessary.	July 2003
Would it be acceptable to introduce a level of sub-folders not described in the eCTD specification to assist the submission construction process? This question was generated by change request 00140	Yes	July 2003
Should bookmarks be presented expanded or collapsed? Should bookmarks for tables and figures be separate structures? This question was generated by change request 00270	Insufficient experience is available across agencies to provide any formal guidance on this. It might not be considered appropriate to have all the bookmarks open since, in some instances, these can be so numerous that they are not useful to the review and it can affect 'refresh' time in a web-browser. Equally, it is probably not useful to have the bookmarks fully closed, since the reviewer would always have to open them. It is recommended, therefore, that the applicant considers the usefulness to the reviewers of how to present bookmarks and has some level of consistency across similar document types within the submission.	July 2003
Can clarification be provided for what should be included as values for the 'font library' attribute? This question was generated by change request 00300	At present, no agency intends to make use of this attribute and therefore provision of guidance is not necessary.	July 2003

Are .tiff files an acceptable format for provision within an eCTD submission or should they be converted to .pdf? This question was generated by change request 00350	The .tiff file type is not supported within the eCTD specification. The section in the specification should be consulted (Appendix 7) relating to acceptable formats.	July 2003
When using the 'delete' operation attribute a checksum is required. Since no file is being provided to assign a checksum to, how should this checksum attribute be used? This question was generated by change request 00130	It is recommended that a null entry be made in the checksum attribute, i.e., double quotation marks with no entry between (“”).	July 2003
Is it feasible for legacy reports to continue to be submitted as a single file/document without being split into separate files/documents as per the M4 Organisation Granularity Annex. Is there a specific date from which all reports should be structured in the M4 Organisation Granularity Annex described way? This question was generated by change request 00460	For study reports that have already been produced or are currently in the process of production, it is considered acceptable to submit these as a single file if this is the way that they have been created. It is recommended that new reports be created utilising the granularity described in the M4 Organisation Granularity Annex.	November 2003
Is the file name for an individual file fixed from beginning to end of life cycle? This question was generated by change request 00590	No, except for names predefined in the eCTD specification or regional guidance, e.g. index.xml.	June 2004
Is the operation attribute for the regional (module 1) backbone xml file always new? This question was generated by change request 00600	Refer to regional guidance.	June 2004

According to ICH E3 Structure and Content of Clinical Study Reports, the case report forms should be located in Appendix 16.3, the individual patient data listings in Appendix 16.4 and the publications and literature references in Appendices 16.1.11 and 16.1.12 respectively. The CTD organization provides locations for case report forms and individual patient data listings in Module 5.3.7 and for literature references in Module 5.4. Where should these items actually be placed in the CTD and the eCTD? This question was submitted to the CTD Implementation Coordination Group.	~~The treatment in the CTD and the eCTD is different. For the eCTD:~~ ~~PDF files for case report forms and individual patient data listings should be organised by study in the folder for Module 5.3.7. However, in the *index.xml* file the leaf elements for the case report forms and individual patient data listings should be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element can be placed under the heading 5.3.7 Case Report Forms and Individual Patient Data Listings. Datasets, if required by the region, should be organised according to regional guidance.~~ ~~Files for publications and literature references should be located in the folder for Module 5.4. However, in the *index.xml* file the leaf elements for the publications and literature references should be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element~~	June 2004 **October 2006**
If an applicant submits an eCTD using Specification v3.0, how is forward compatibility with version 3.2 assured? This question was generated by change request 00540	The recommendation is that applicants use the ID, even if using 3.0, to avoid future compatibility problems; For previously submitted files, consult with the Regulatory Agency to ascertain how to resolve the lifecycle issue.	June 2004

Is it expected that one would stay with a given DTD version for the duration of an application, so that as long as submissions are made to the same application, one would use the same DTD version as for the original submission? Would - on the other hand - the expectation be that new versions of the DTD are applied within a certain time period, across all submissions regardless of whether they are new or ongoing? Also, if there is a need to change DTDs, how will the agency viewing tools present the cumulative view if there is a structural change to the submission eg. renaming of old sections, introduction of new sections etc. The question was generated by change request 00690	Applicants are expected to use the current DTD as accepted in the individual regions. The M2 Expert Working Group and the agencies of the three regions will provide guidance on when to use new releases. The timing of the implementations of new releases will be determined as required. Regulatory changes (e.g. changes in the CTD) might have to be implemented immediately, while technical changes might be delayed to major new releases.	November 2004
Clarification should be provided by all ICH regions as to whether node extensions can be used in Modules 2-5 The ICH spec allows node extensions to be used in Modules 2-5 and their use in Module 1 is a regional matter. FDA states that node extensions are not supported in any part of the submission and this therefore invalidates the ICH spec. Experience on production of submissions for Europe demonstrates that node extensions are required to deliver a navigable structure for Modules 4 and 5. At present this means that eCTDs are not re-usable across regions and thus will create significant amounts of rework for industry. FDA should accept node extensions in Modules 2-5. The question was generated by change request 00560	The use of node extensions should be discussed with FDA on a case by case basis. Other regions are able to accept appropriate use of node extensions in compliance with the eCTD specification (i.e. their use is discouraged unless there is no other feasible means to submit the information). Refer to EU and MHLW regional guidance for specific instances where it can be used.	November 2004 May 2005

Can a single, global eCTD submission be constructed and transmitted to multiple regions, with each regional authority ignoring or deleting other regions' submission material? The question was generated by change request 00700	This is not advised.	May 2005
Are applicant provided style sheets allowed? The question was generated by change request 00710	Consult regional guidance	May 2005
Is a regional MD5 checksum file (xx-regional-md5.txt) needed? The question was generated by change request 00720	Not needed, index.xml includes the checksum for this file.	May 2005
Japanese characters are 2 bytes. Can 64 characters still be used for file/folder names in Japanese? The question was generated by change request 00730	The Specification 3.2 does not allow for Japanese characters in folder and file names.	May 2005
Do submission sequence numbers have to be consecutive, i.e., 0005 must be submitted after 0004? The question was generated by change request 00760	For Japanese submissions, sequential numbering is required. For all other regions, it is preferred, but not required. For all regions, sequence numbers should be unique within the overall application.	May 2005
Can the operation attribute ‘new’ be used in subsequent submissions where there is already a file in the same node? The question was generated by change request 00820	Yes, but there might not be many opportunities in Modules 2-5, where this could apply. This might be more applicable in Module 1 with items such as cover letters and application forms. Refer to table 6-3 of the Specification 3.2 for the appropriate use of the operation attribute.	May 2005
Can further clarification be provided on the related sequence element? The question was generated by change request 00890	Related sequence is used differently across the regions. Consult regional guidance for details.	May 2005

From the eCTD experience of the IWG, what parts of the Specification are commonly misinterpreted that would prevent my eCTD message from being viewed by another applicant/regulator? This question was generated by change request 00580	Based on experience, there have been different interpretations of the eCTD Specification that have prevented timely exchange of eCTD submissions. Those creating and viewing eCTD messages should adhere to the eCTD Specifications (ICH and regional) and consult with regional authorities to avoid these problems. The items in the following list already exist in the Specification 3.2, but have been summarized here to alleviate these problems. Adherence to these items is technically necessary to exchange eCTD messages. Extra controls might hinder the exchange of eCTD messages. The IWG will continue to monitor eCTD implementation to provide additional clarity. Items 12 and 20 were updated on May 11,2007	May 2005 May 2007
The eCTD specification supports the ability to refer to a previously submitted file, for example, by including in sequence 0005 a leaf with Operation Attribute of 'new' that refers to a file submitted in 0000. Is it possible to indicate to the reviewer that they have already received and reviewed the file before? Could an additional Operation Attribute be considered for this type of cross-referenceing or re-use? The question was generated by change request 01080	At this stage of the implementation of the eCTD, the four Operation Attributes (new, append, replace and delete) will remain and not be added to. With the existing specification it is technically possible to determine that a file is not in the current sequence, but is from a previous sequence. Suppliers of eCTD viewing tools are encouraged to develop a visual way of displaying the difference between a leaf referring to a file in the current sequence and a leaf referring to a file in a previous sequence. In this circumstance note that the list of items to be checked under Q&A No. 36 should allow for the xlink:href to refer to files in another sequence and not prevent viewing of the eCTD by another applicant/regulator. Refer to regional guidance with respect to the allowance of reference to previously submitted files.	November 2005
The eCTD specification recommends not including a file more than once within a sequence. If multiple leaf references are intended to display a file in multiple locations within the eCTD, is it possible to indicate to the reviewer that this file is referred to more than once in the sequence, which might alert the reviewer that the file is displayed multiple times? Could an additional Operation Attribute be considered for this type of cross-referencing or re-use? The question was generated by change request 01080	At this stage of the implementation of the eCTD, the four Operation Attributes (new, append, replace and delete) will remain and not be added to. With the existing specification it is technically possible to determine that a file is linked to by multiple leafs in the same sequence. Suppliers of eCTD viewing tools are encouraged to develop a visual way of display when this occurs.	November 2005

In Modules 2-5, instead of submitting pdf documents is it possible to submit XML documents? The question was generated by change request 01250	It is recognized that there is a general trend towards describing the contents of documents with XML. However, the current specification supports only the use of XML for structured information. It can be interpreted from this that the submission of summaries, reports and other narrative documents in XML format is not currently supported by the specification. The specification also states that regulatory authorities and applicants could agree to use other formats regionally (including uses of the common formats in a different way from the above). Thus, if an applicant wishes to use XML for narrative documents, they should liaise with their regional regulatory authority, understanding that other regulatory authorities may not accept these XML files. In the longer term, M2 may adopt a standard for describing narrative documents with XML.	November 2005
Can PDF version 1.4 be used across all regions?	~~The eCTD specification will be changed at the next release to indicate that PDF version 1.4 is the only version acceptable in all regions. Applicants should transition as soon as possible.~~ This answer has been withdrawn. See Q&A No. 46.	Nov-2005 May-2007
The M4 Granularity document requires that all pages of a document should include a unique header or footer that briefly identifies its subject matter. With the eCTD there is a significant amount of metadata available to the reviewer to allow easy identification of the document concerned without the necessity to place an identifier in the header or footer. Is it necessary to include a unique identifier in an electronic only submission? The question was generated by change request 1310.	When an electronic submission is made, there are still circumstances where it is appropriate to have a unique identifier on each page (header or footer) of the document, e.g. when the document is printed or multiple documents are viewed on screen at the same time. The unique identifier does not necessarily have to contain the CTD section identifier or other metadata. It should be sufficient to identify the general subject matter of the document, e.g. study identifier, batch number.	June 2006

According to ICH E3 Structure and Content of Clinical Study Reports, the case report forms should be located in Appendix 16.3, the individual patient data listings in Appendix 16.4 and the publications and literature references in Appendices 16.1.11 and 16.1.12 respectively. The CTD organization provides locations for case report forms and individual patient data listings in Module 5.3.7 and for literature references in Module 5.4. Where should these items actually be placed in the CTD and the eCTD? This question was submitted to the CTD Implementation Coordination Group.	Case report forms, data sets and individual patient data listings should be organized according to regional guidance. Files for publications and literature references should be located in the folder for Module 5.4. However, in the *index.xml* file the leaf elements for the publications and literature references should be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element should be placed under the heading for 5.4 Literature References.	Oct-06
Please, confirm that a single file can replace multiple files from various previous sequences.	No, a single leaf operation can only target a single leaf element. It is important to distinguish between leaf elements and files. eCTD specifications describe the management of leaf elements, not files.	May-07
Please, confirm that a single file in an eCTD lifecycle can be replaced multiple times	No, once a leaf element has been replaced in an application it is no longer considered current. Only the current leaf should be replaced in a subsequent sequence.	May-07

How to update the eCTD metadata if the name of an excipient changes, as indicated in e.g. the USP/NF or European Pharmacopoeia? The names of excipients have to be incorporated in the metadata of an eCTD. It is even reflected in the folder names under 3.2.P.4. During the lifecycle of a medicinal product the name of a particular excipient used may change over time without alterations being made to the formulation. How to deal on the level of the eCTD with alterations in the name of a particular compendial excipient? How to deal on the level of the eCTD with alterations in the name of a particular noncompendial excipient?	The eCTD specification does not have an explicit mechanism for changes to attributes during life cycle. As a work around, applicants would delete all leafs within the element with the incorrect excipient attribute and re-submit them within an element with the corrected excipient attribute. This work around would apply to both compendial and non-compendial excipients. Please consult your agency before performing this operation.	May-07
ICH eCTD Question Number 40 asks whether it is acceptable to submit PDF V1.4 files across all regions. Although the answer given is in the affirmative, it actually goes much further than mere 'acceptability' by appearing to make V1.4 mandatory for eCTDs. Shouldn't V1.4 be 'acceptable' or perhaps 'preferred' (if justified) rather than 'mandatory'?	Q&A 40 is being retired and a new Q&A is created to read: all regions have agreed to accept PDF 1.4. Please consult regional guidance to submit other versions of PDF.	May-07
Is PDF/A-1 an acceptable PDF file format for documents submitted in an eCTD?	PDF/A-1 is an archive format and does not meet the ICH review needs for use with an eCTD.	May-07