



**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.**

V1.0

February 2006

Table of Contents

Practical guidance.....	1
1. Document Control	3
2. Change Record	3
3. Reviewers.....	3
4. Distribution	3
5. Introduction	4
5.1. Background	4
5.2. Aims of Introducing the eCTD.....	4
5.3. Rationale.....	5
5.4. Purpose of this document	6
5.5. Scope	6
6. Definitions	6
7. Guidelines.....	7
7.1. Printing by Agency or Applicant.....	7
7.2. Number of Printed Paper Copies Required	7
7.3. Structure of the Printed eCTD.....	8
7.4. Provision of Tabs for the Printed eCTD.....	8
7.5. Printed Table of Contents (ToC)	9
7.6. Specification of Cross-Reference Strings.....	10
7.7. Printed Application Form.....	11
7.8. Documents Available on Request	11
7.9. Reference to Previous Submissions.....	11
7.10. Lifecycle Attributes of the eCTD	11
ANNEX I.....	13

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.

1. Document Control

2. Change Record

Version	Date	Author(s)	Comments
0.1	November 2004	Joint TIGes-Industry Sub-Group	Draft
0.2	March 2005	Joint TIGes-Industry Sub-Group	Draft
0.3	September 2005	Joint TIGes-Industry Sub-Group	Draft
1.0	December 2005	Joint TIGes-Industry Sub-Group	Final
1.0	February 2006	NtA-TIGes Interlinking Comments	Final

3. Reviewers

Version	Name	Organisation
0.1	Joint TIGes-Industry Sub-Group	TIGes-J
0.2	EMEA/NCAs	EU
0.3	Joint TIGes-Industry Group	TIGes-J
1.0	Joint TIGes-Industry Group	TIGes-J

4. Distribution

Version	Date	Name	Status
0.1	November 2004	Joint TIGes-Industry Group	Reviewed
0.2	June 2005	EMEA/NCAs	Reviewed
0.3	September 2005	TIGes/Joint TIGes-Industry Group	Reviewed
1.0	December 2005	TIGes/Joint TIGes-Industry Group	Adopted
1.0	December 2005	TIGes/NtA-TIGes Interlinking/JIGes	Submitted

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.

5. Introduction

5.1. Background

In the context of working towards global harmonisation in the interpretation and application of technical guidelines or requirements for product registration, an expert working group of the ICH¹ M2 agreed in September 2002 on a specification for an electronic Common Technical Document (eCTD) to be used for marketing authorisation applications. The harmonised text of the eCTD specification has now moved into the final step of the process, which is the regulatory implementation. This is carried out according to the same national/regional procedures that apply to other regulatory guidelines and requirements, in the European Union, Japan and the USA.

The EU regulatory community is currently in a period of transition. From 1st June 2003, applicants have the option of submitting an eCTD in parallel with the paper submission (CTD) to the Competent Authorities. Following this transition period, marketing authorisation applications shall be valid whether submitted on paper, or as a set of electronic files, provided that the legislation and guidelines governing the content, format and processes for such submissions in force at the date of submission have been complied with.

It is foreseen that the transition period will extend until November 2006 for the EMEA. The Heads of Agencies have agreed on being ready to accept pure electronic submissions by the end of 2009.

During the transition period, however, before such time as appropriate regulations in Electronic Archiving Law come into force, the official submission required for validation of any application made through the Centralised Procedure and National Procedures for the majority of Member States remains that made on paper, and an eCTD submission alone cannot be considered legally valid. eCTDs are welcomed, however, to enable applicants and agencies alike to gain experience in electronic submission processing and review, and to develop the expertise necessary for eventual full implementation of the eCTD.

5.2. Aims of Introducing the eCTD

The ultimate aims of the European regulatory community, in accepting electronically submitted information using the eCTD, will be to facilitate the review process and ease practical difficulties. These aims may be further refined as follows:

- The facilitation of the review process through:
 - Easy viewing;
 - Legibility;
 - Printer friendly formats;
 - Easy and rapid navigation through a table of contents, and links within files;
 - The ability to search (the submission metadata as well as narrative text, and across submissions);
 - The ability to transcribe all types of information for review and analysis; and
 - Improved access to the current information on the product through automatic update

- The easing of practical difficulties through:
 - The reduction of physical paper flows;

¹ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: <http://www.ich.org>

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.

- The reduction in the requirement for physical storage space during review;
- The reduction of the requirement for physical archiving space; and
- The ability to identify and call up archived information easily and rapidly through electronic filing.

5.3. Rationale

During the eCTD transition period, for centralised procedures the requirement to submit paper copies in accordance with the EMEA’s published submission guidance² remains. For the moment, the EMEA’s policy is that applicants will have the option of submitting an eCTD in parallel with the paper submission. During this period, the official submission shall be the paper submission.

For national procedures, MRP and DCP the relevant national requirements, based on national legislation, have to be taken into account.

It is intended that, following the transition period, all Competent Authorities shall be in a position to accept electronic-only submissions of applicant’s information. In order to reach this state of full eCTD implementation, the following are necessary:

- Appropriate archiving law and electronic records management policy in place to ensure appropriate and sustainable electronic archiving,
- Sufficient experience gained to enable validation, processing and review to be carried out using eCTD submissions only
- Appropriate tool(s) implemented to receive, validate, store and make available for review marketing authorisation applications and supporting documents submitted electronically by applicants using the eCTD
- Development of business processes/SOPs/workflow organisation
- Appropriate tool(s) in place to support sustainable lifecycle management for a product.

Until such time as these measures are in place, however, a combination of parallel paper and eCTD submissions must necessarily be the working scenario whilst eCTD implementation progresses. It is important to stimulate the submission of eCTDs in order to gain sufficient experience and develop requirements, and progress organically with eCTD implementation.

Currently, paper submissions are produced following the paper-based CTD format, necessitating production of two essentially different submissions if an eCTD is to be submitted in addition. The considerable further work required and associated costs implied here are thereby impeding the implementation of the eCTD and its adoption by industry.

It is mutually accepted that the only pragmatic solution is to enable applicants to use the eCTD as the antecedent submission, to be printed out to produce the official paper submission. However, initial experiences indicate that simply printing the eCTD as it stands produces a paper submission that in some ways is unacceptable to regulators due to difficulties with navigation and review. This is largely an inevitable consequence of reproduction in paper of what are intended to be electronic navigational aids. It must be accepted that the paper submission will still be used for review in some cases, where at this stage appropriate viewing software may not be available.

There is a common understanding that this is an issue, and this interim guidance is required as to additional support to be provided for the presentation of the printed eCTD. In this way, additional work for applicants when submitting ‘experimental’ eCTDs is reduced, and eCTD implementation and experience can be further developed whilst still producing a paper submission that has a sufficient legal basis and is acceptable for use from a regulatory perspective.

² www.emea.eu.int: Human medicines; Pre-submission guidance; List of questions and answers; question 23

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.

The recommendations detailed in this guidance are of importance to circumvent the necessity for two publishing processes, and to increase incentive for industry and Regulatory Agencies to increase the number of eCTDs submitted and processed.

5.4. Purpose of this document

In preparing this guidance document, experience gained to date with eCTD submissions has been taken into consideration.

The goals of this guidance are to enhance the ease of receipt, processing and review of eCTD submissions and associated paper submissions at the EMEA or National Competent Authorities and to ensure efficient submission handling. Specifically, this guidance makes recommendations regarding the presentation of the paper submission that is provided by the applicant when an eCTD submission is also provided and acts as the ‘source’ submission for all hard copies.

5.5. Scope

The scope of this guidance extends to all eCTDs and associated paper submissions that are submitted to the EMEA and/or National Competent Authorities through a centralised procedure, national, mutual recognition or decentralised procedure, namely:

- New applications;
 - Full applications
 - Bibliographical applications
 - Generic, hybrid or biosimilar applications
 - Informed Consent Applications
 - Supplemental Information
 - ASMF
- Plasma Master File, Vaccine Antigen Master File
- Variations and extensions;
- Art 61(3) Notifications and corrigenda;
- Follow-up measures;
- Specific Obligations;
- Annual Reassessments;
- Renewals.

6. Definitions

<i>Term</i>	<i>Definition</i>
Applicant	A pharmaceutical company or its agent that is submitting information in support of an <i>application</i> .
Applicant’s information	Regulatory information submitted by an <i>applicant</i> for a marketing authorisation that falls within the scope of this guidance document
Application	Structured dossier compiled by a pharmaceutical company or its agent in compliance with European legislation and guidelines in order to seek a in order to seek a marketing

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.

<i>Term</i>	<i>Definition</i>
eCTD	authorisation or any amendments thereof. An application may comprise a number of <i>submissions</i> . Electronic Common Technical Document
NtA	Notice to Applicants
Procedure	Marketing Authorisation Procedure: Centralised, Mutual Recognition and National Procedures, and the Decentralised Procedure, Variation procedure. Renewal procedure.
Submission	A single set of information and/or documents supplied by the <i>applicant</i> as a part of, or the complete, application.
TIGes	Telematics Implementation Group for eSubmissions

7. Guidelines

Recommendations on the generation and presentation of the ‘paper eCTD’ can fall into several areas, and are addressed in the sections below.

7.1. Printing by Agency or Applicant

In the event of an electronic archiving policy that rendered electronic submissions legally valid, any printed material would serve solely as a review aid. As such, the leaf files could be printed by applicants or regulators on an ad hoc basis.

Depending on the national legal requirements in most of the EU-member states during the eCTD transition period, the paper submission is the legally valid submission, and as such the applicant is solely responsible for the integrity and completeness of the material submitted, and also to reproduce where possible the navigational aids that form the subject of much of this guidance. Furthermore, it is the responsibility of the applicant, assumed to have superior printing capacity, to utilise this capacity to produce a valid submission on paper.

It is therefore recommended that applicants remain responsible for printing and submission of the paper copy. The quality and quantity of these paper copies is addressed in subsequent chapters of this guidance.

7.2. Number of Printed Paper Copies Required

There is currently no unified European regulatory position on electronic archiving, and each National Competent Authority has addressed the legality of electronic data as archive to a different degree. For this reason, this guidance does not present proposals as to the number of paper copies of the dossier, or as to which modules, should be submitted along with the eCTD.

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.

EMA pre-Submission and Post-Authorisation Guidance on paper copies to be submitted for the Centralised Procedure should be followed in this context. This guidance is to be found at: <http://www.emea.eu.int/hums/human/presub/q23-2.htm> (Pre-Submission) <http://www.emea.eu.int/hums/human/postguidance/1998403en.pdf> (Post-Authorisation)

For national requirements regarding the submission of a reduced number of paper copies of Modules modules when accompanied by an eCTD - NtA Volume 2A Chapter 7 should provide sufficient information.

7.3. Structure of the Printed eCTD

The current eCTD structure, as defined in the current EU Module 1 specification for eCTD, should not deviate from the adopted CTD structure.

The eCTD specification v1.0 provides guidance that is complementary to the CTD guidance, and that refers to the technical implementation. There should be no contradiction between CTD and eCTD guidance.

The structure of a printed copy of the eCTD should be in accordance with the sequence of documents as referenced in the xml backbone of the eCTD (specification v1.0). This sequence of documents should be in line with paper CTD guidance.

Where previous eCTD specification v0.9 is used, the Cover Letter, belonging there to eCTD section 1.7.1, should be moved and placed as the first document in Module 1 of the printed eCTD for ease of review.

There should be one Cover Letter included in the paper dossier, (and this should not contain details of the MD5 checksum for the eCTD).

Where a document appears in several relevant locations in the eCTD backbone, it should only appear once in the paper output, in the most appropriate location. Consideration of the chosen location of the document is important.

7.4. Provision of Tabs for the Printed eCTD

It can be assumed, in consideration of the points made in section 3,2 of this guidance, that the paper eCTD will serve as the legal archive copy of the dossier within many regulatory agencies at this stage.

It must be assumed also that this paper eCTD may also be used in some cases for review of the dossier. A paper copy can be seen to be a more convenient medium for the review of some individual files, whereas navigation through the dossier as a whole is facilitated by the eCTD through the use of hyperlinks etc.

In the paper copy of an eCTD, therefore, identifiers detailing the eCTD section number and name should be used on a tab that precedes the documents within each section, to facilitate navigation to those documents in the paper dossier if necessary.

For clinical and/or non-clinical study reports and appendices, further sub-division is required within a section to aid navigation to individual reports.

One tab per eCTD section in modules 1, 2 and 3 should be provided, down to 4th level section numbering

In modules 4 and 5, one tab per study report is required

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.

Slip Sheets are optional, e.g. for a large number of literature references

The cover of any binder should indicate the first and last section number contained (e.g. m-3-2-s-1-1-nomenclature/m-3-2-r-regional-information for Module 3 Volume 1).

7.5. Printed Table of Contents (ToC)

A Table of Contents (ToC) can be said to provide the following:

- An ordered enumeration of all questions or subjects (or documents) that are included in a document (or dossier)
- An indication of where that subject or document can be found. This indication is related to the way in which the content of the document/dossier is organised (by volumes, modules, sections, documents, chapters).

The NtA guidelines³ provide an indication only of where the ToC should appear in the paper CTD, namely:

- in section 1.1 (a table of contents for the whole dossier)
- in section 2.1 (a table of contents for Modules 2, 3, 4 and 5)
- in section 3.1 (a table of contents for Module 3)
- in section 4.1 (a table of contents for Module 4)
- in section 5.1 (a table of contents for Module 5)

The ICH M4 recommendations on the organization of a paper CTD⁴ state:

“All Table of Contents title entries should either correspond to heading names and section numbering as defined in the M4Q guideline, or to identifiers appearing on tabs (for a paper drug submission only), preferably by their full title, which should easily identify any abbreviated title that might be used on the corresponding tab. The Table of Contents should not specify any page numbers.”

Furthermore, the ICH eCTD specification⁵ defines the ToC in an eCTD in the following way:

“The XML eCTD DTD (Document Type Definition) defines the overall structure of the submission. The purpose of the XML backbone is two-fold: (1) to manage meta-data for the entire submission and each document within the submission and (2) to constitute a comprehensive table of contents and provide corresponding navigation aid. The XML eCTD instance covers the entire submission including all hierarchical levels and includes references to each individual file.”

The eCTD does not include a separate ToC document.

The ToC for a printed eCTD should fulfil the objectives detailed above, and therefore a printed output of the XML backbone should serve as a ToC comparable to that of the paper CTD.

The index.xml backbone, as viewed using a style sheet, and converted to PDF, should be printed and should serve as the ToC in the paper eCTD. This comprehensive ToC for all modules should be placed before each module of the printed submission.

The ToC should be expandable and collapsible

Where possible, a standard stylesheet should be used for consistency across regions.

³ Notice to Applicants, Volume 2B, Presentation and format of the dossier – CTD – Edition July 2003

⁴ Annex to the M4 Organisation: Granularity – Corrigendum – January 16, 2004, ICH.

⁵ ICH M2 EWG – Electronic Common Technical Document Specification, v3.2, February 4 2004

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.

This printed ToC should contain the following elements:

- **The section number and section name, as an entry for each file of the eCTD**
- **The volume number and the identifier appearing on the tab sheet⁶, as a way of indicating the place where one can find the corresponding document (this recommendation is modeled on the guidance for submitting some parts of an eCTD dossier on paper).**
- **(If tab sheets are not included in the printed eCTD dossier): the section number that will be detailed either on the footer or on the header of each document.**

Volumes can be numbered from 1 to n per module or from 1 to n through the submission as a whole (i.e. not numbered per module). To facilitate the creation of this table of contents, there should be only one table of contents for the whole dossier. The same table of contents should be placed before each module.

Since each individual file in the eCTD as well as in the printed output will be paginated from 1 to n, no indication of the page number is needed in the ToC.

See Annex I, ToC from an index .xml viewed through a style sheet and converted to PDF, for an example of an acceptable ToC.

7.6. Specification of Cross-Reference Strings

A link or cross-reference is characterized by 3 elements:

- A source which contains the anchor of the link and a cross-reference string describing the target (1)
- The link itself, connecting the source and the target (2)
- A target (3), i.e. annotations, related sections, publications, appendices, tables, figures or potentially the top of the page with one of these components, based on the linking technology

It is of course not always necessary to include the cross-reference string in an eCTD, as navigation can be made directly to the target using the electronic hyperlink.

For the printed paper eCTD, however, a cross reference string is necessary, as the paper dossier must specify a target in such a way that it is easy for the reviewer to retrieve.

For cross-references outside a document, the CTD section or study identifier must be referenced. The notation must contain at least the target name and eCTD element number (for instance 3.2.P.4.3, Table 4.3.1 Descriptive Data). Ideally the cross-reference should include the page within the eCTD element, although this is optional.

For cross references within a document, the document section number or table should be referred to, as the document itself will have a ToC and will be paginated

The correlation between eCTD element numbers and Volume numbers should be seen in the ToC.

⁶ “During the transition to fully electronic submissions of the CTD, some regions will accept that some sections can be submitted as paper only. Please refer to regional guidance. These sections should be identified in the XML eCTD instance by including a PDF file in the instance that describes the content and location of the paper section. For example, the PDF file might consist of only one page with the name of the CTD document and the physical volume number and tab identifier.”

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.

7.7. Printed Application Form

An application form can currently be provided either by using the templates supplied by the NtA for new applications,⁷ variations,⁸ and renewals.⁹ (Further to this approach, it is intended that for subsequent versions of the EU M1, it will be possible to build an application form using XML according to the Electronic Application Form Specification v1.0¹⁰ and produce a printable output using an appropriate tool.)

In the paper representation of the eCTD, the application form should be rendered from text to PDF and printed accordingly.

7.8. Documents Available on Request

For ease of handling and manageability, some documents relevant to a submission may not be included in the eCTD, but instead may be available on request. These documents can include literature references and report appendices. A harmonised approach is required to the presentation of these documents available on request.

For study report appendices, one of two approaches can be taken:

- A. separate file is placed in section 5.3, presenting a list of all documents available on request.**
- B. Section 5.1 eCTD comprehensive Table of Contents contains a comprehensive list of all reports and annexes, and is annotated to indicate which of these reports are available on request.**

For literature references, a list of all references should be provided, and those literature references that are included in the dossier should be hyperlinked (with cross reference string) to the reference itself, while those available on request should be simply listed. The reference is indicated as available on request by the lack of cross-reference and hyperlink. The approach chosen by the Applicant to address documents available on request, as first agreed with the agency, should be detailed in the Cover Letter.

7.9. Reference to Previous Submissions

The references to previous submissions that can be used for automated lifecycle management of submissions present added value in the eCTD only, as they are interpreted and processed by tools to present a history of the information on a medicinal product. The presentation of these references in the printed version of the eCTD is therefore not relevant.

7.10. Lifecycle Attributes of the eCTD

⁷ http://pharmacos.eudra.org/F2/eudralex/vol-2/B/PartIA_200307.doc
⁸ http://pharmacos.eudra.org/F2/eudralex/vol-2/C/mr-renewal-form_2004_01.doc
⁹ http://pharmacos.eudra.org/F2/eudralex/vol-6/newdoc/newvarform_%20250703.doc
¹⁰ <http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm>

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.

The attributes that can be used for automated lifecycle management of submissions (operator and sequence) present added value in the eCTD only, as they are interpreted and processed by tools to present a history of the information on a medicinal product.

The presentation of these elements in the printed version of the eCTD is therefore not relevant.

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.

ANNEX I

Example ToC based on index.xml viewed through Internet Explorer and converted to PDF

m2-7-2-summary-of-clinical-pharmacology-studies	
Summary of Clinical Pharmacology Studies	+
m2-7-3-summary-of-clinical-efficacy-confusion	Volume 3
Summary of Clinical Efficacy - confusion	+
m2-7-3-summary-of-clinical-efficacy-awareness	
Summary of Clinical Efficacy - awareness	+
m2-7-4-summary-of-clinical-safety	
Summary of Clinical Safety	+
m2-7-5-literature-references	Volume 4
Literature References	+
m2-7-6-synopses-of-individual-studies	
Synopses of Individual Studies	+
m3-2-s-1-1-nomenclature	Volume 1
Nomenclature (eurotriptan maleate, eurofact)	+
m3-2-s-1-2-structure	
Structure (eurotriptan maleate, eurofact)	+
m3-2-s-1-3-general-properties	
General Properties (eurotriptan maleate, eurofact)	+