Practical Guidance
For the Paper Submission of Regulatory Information in Support of a Marketing Authorisation Application When Using an eCTD or a NeeS as the Source Submission.

v2.0

March 2010

Please note that this document is being published on the EMA eSubmission website so that both agencies and applicants can better understand the implications of submitting a simple paper dossier in support of a submission provided in eCTD or NeeS format. Dossiers printed in accordance with this guidance may be more difficult to navigate than a dossier printed using ICH CTD guidance. However, the intention is that the production of paper as described herein will ease the burden on applicants who are providing an electronic dossier, and encourage assessors to use the electronic format provided for the review.

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Document Control

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
1.1	December 2009	EFPIA eCTD Topic Group	Draft
2.0	March 2010	EFPIA eCTD Topic Group	Draft for testing

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
2.0	Joint TIGes-Industry Group	TIGes-J

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
2.0	March 2010	TIGes/NtA-TIGes Interlinking/JIGes	Adopted for test use

Definitions

Term	***Definition***
Applicant	A pharmaceutical company or its agent that is submitting information in support of an ***application***.
Applicant's information	Regulatory information submitted by an ***applicant*** for a marketing authorisation that falls within the scope of this guidance document
Application	A collection of documents compiled by a pharmaceutical company or its agent in compliance with European legislation and guidelines in order to seek a marketing authorisation or any amendments thereof. An application may comprise a number of ***submissions***.
eCTD	Electronic Common Technical Document
NeeS	Non –eCTD Electronic Submission
NtA	Notice to Applicants
Procedure	A Community registration procedure for the authorisation of medicinal products in the European Community. There are 4 types of procedures that operate within the EC: the Centralised, Mutual Recognition, Decentralised and National Procedures.
Submission	A discrete package of information and/or documents supplied by the ***applicant*** to initiate or supplement an Application.
TIGes	Telematics Implementation Group for eSubmissions – EU body responsible for the development of eCTD or NeeS and eSubmission regional standards and their implementation

1 Background

Although the eCTD format is now accepted in lieu of paper in the Centralised Procedure and eCTD or NeeS formats are accepted in many EU member states for submissions in MRP/DCP and National Procedures, a paper copy of the dossier is still a legal requirement in some countries. This document provides guidance on how to create a paper dossier where the primary (original) dossier is in the eCTD or NeeS format.

2 Rationale

In the past, paper submissions were produced following the paper-based CTD format, effectively necessitating the production of two different submissions if an eCTD or NeeS was to be submitted. The considerable additional work (and associated costs) entailed in producing a submission in two fundamentally different formats significantly impeded the implementation and adoption of electronic submissions by industry.

It is mutually accepted that the only pragmatic solution to this problem is to allow applicants to use the eCTD or NeeS as the antecedent submission, from which the official paper submission is then printed. Printing the eCTD or NeeS as per the directions in this guidance will fulfil the requirements of regulatory authorities requiring paper for legal or archiving purposes. Note that paper-based navigation and review aids (eg, Tables of Contents that reference paper volumes; tabs etc) will therefore not be included, as the paper copy is not intended to support dossier review.

3 Purpose of this document

The goals of this guidance are to enhance the ease of receipt, processing and review of eCTD or NeeS submissions and associated paper submissions in National Competent Authorities (NCAs) and to ensure efficient submission handling. Specifically, this guidance makes recommendations regarding the presentation of the paper submission that is provided by the applicant in addition to an eCTD or NeeS submission.

4 Scope

The scope of this guidance extends to all submission types in all European procedures where there is an NCA requirement for a paper submission to be submitted in addition to an eCTD or NeeS. Recommendations on the generation and presentation of the paper accompanying an eCTD or NeeS submission are addressed in the sections below.

5 Printing by Agency or Applicant

Many EU countries recognise the electronic submission in eCTD or NeeS format as the legally valid submission - any printed material serves solely as a review aid and thus has no legal standing. As such, the content of an eCTD or NeeS can be printed by applicants or regulators on an ad hoc basis.

However, where the paper submission is the legally valid submission, or where local regulations require that a paper dossier is provided, then it is the responsibility of the applicant to produce a valid

submission on paper, and the applicant is solely responsible for the integrity and completeness of the material submitted.

6 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 an archive copy – 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 or NeeS. Summary of this information is available on the CMD(h) website, under Human Medicines > CMD(h) > Procedural Guidance > eSubmissions. (http://www.hma.eu/277.html)

7 Structure of the Printed eCTD or NeeS

The eCTD structure, as defined in the current EU Module 1 specification for eCTD and ICH eCTD Guidance, does not deviate from the adopted CTD structure. The eCTD specification provides guidance that is complementary to the CTD guidance, specifically referring to the technical implementation. Similarly, the NeeS specification is derived from the eCTD. Therefore, there should be no contradiction between CTD and eCTD or NeeS guidances.

The structure of a printed copy of the eCTD or NeeS should be in accordance with the sequence of documents as referenced in the XML backbone of the eCTD or the overall Table of Contents (TOC) of the NeeS. This sequence of documents should be in line with CTD guidance. 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 or NeeS TOC, it should only appear once in the paper output, in the most appropriate location. Consideration should be given to the most logical location of the document.

8 Provision of Tabs for the Printed eCTD or NeeS

As the paper copy is being provided solely to support legal and/or archiving requirements, and not to support the review of the dossier, paper-based navigation aids such as tabs should not be provided.

9 Printed Table of Contents (ToC)

9.1 eCTD

For eCTD, the index.xml and eu-regional backbones, as viewed using style sheets and converted to PDF, should be printed and should serve as the ToC in the accompanying paper dossier. For module 1, eu-regional.xml should be printed via the stylesheet to create the ToC. The comprehensive ToC for all modules based on index.xml should be placed before m2, m3, m4 and m5 of the printed submission. The same table of contents should be placed before each module – there is no need to create module specific ToCs. This printed ToC does not need any extra work over and above application of the style sheet to the index.xml or eu-regional.xml (for module 1), and will therefore not contain information relating to which printed volume the content referred to can be found within.

9.2 NeeS

The NeeS TOCs are printed directly (either a single ctd-toc.pdf for the entire submission or the individual module TOCs - m*x*-toc.pdf). Again, there is no need for any extra work over and above printing of the relevant electronic files, and the resulting ToCs will therefore not contain information relating to numbers of printed volumes.

See Appendix 1 for examples of acceptable ToCs.

10 Headers and Footers

The header and footer information in the printed copy of the dossier should be identical to the information contained in the documents in the eCTD or NeeS, which in turn should comply with the ICH eCTD Specification, version 3.2.2, Appendix 7, or CTD guidance.

11 Printed Application Form

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

12 Reference to Previous Submissions & Lifecycle Attributes

In the eCTD, references to previous submissions or operation attributes in XML leaves can be used for automated lifecycle management of submissions. They are interpreted and processed by eCTD viewing 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 neither relevant nor necessary. The paper needs to be identical in content to the eCTD sequence or NeeS submission, and will not contain content that may be referred to from the submission but provided electronically in a previous submission. If a document is referred to more than once within a submission, it will be printed only once in a location defined by the module folder in which it appears.

13 Labelling of Individual Volumes – Covers and Spines

In the paper version of the eCTD or NeeS, coverboards should include items such as trade name, INN, presentation, strength, submission type, submission date and a volume number per module. There is no requirement to indicate specific sections or documents contained in a volume. Spine labels (if provided) should contain a summary of this information.

Appendix 1 – Example Tables of Contents

Example ToC for paper accompanying an eCTD, based on index.xml viewed through Internet Explorer and converted to PDF.

eCTD DTD version 3.2

- m1-administrative-information-and-prescribing-information
  - eu-regional [new]
- m2-common-technical-document-summaries
  - m2-2-introduction
    - Introduction [new]
  - m2-3-quality-overall-summary
    - m2-3-introduction
      - Introduction [new]
    - m2-3-s-drug-substance [manufacturer: 123] [substance: xyz]
      - Drug Substance xyz [new]
    - m2-3-p-drug-product [manufacturer: 123] [product name: abc] [dosage form: tablet]
      - Drug Product Tablet [new]
    - m2-3-a-appendices
      - Appendices [new]
    - m2-3-r-regional-information
      - Regional Information [new]
  - m2-4-nonclinical-overview
    - Nonclinical Overview [new]
  - m2-5-clinical-overview
    - Clinical Overview [new]
    - Clinical Overview Appendix 1 [new]
    - Clinical Overview Appendix 2 [new]
  - m2-6-nonclinical-written-and-tabulated-summaries
    - m2-6-1-introduction
      - Introduction [new]
    - m2-6-2-pharmacology-written-summary
      - Pharmacology Written Summary [new]
    - m2-6-3-pharmacology-tabulated-summary
      - Pharmacology Tabulated Summary [new]
    - m2-6-4-pharmacokinetics-written-summary
      - Pharmacokinetics Written Summary [new]
    - m2-6-5-pharmacokinetics-tabulated-summary
      - Pharmacokinetics Tabulated Summary [new]
    - m2-6-6-toxicology-written-summary
      - Toxicology Written Summary [new]
    - m2-6-7-toxicology-tabulated-summary
      - Toxicology Tabulated Summary [new]
  - m2-7-clinical-summary
    - m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods
      - Summary of Biopharmaceutic [new]
    - m2-7-2-summary-of-clinical-pharmacology-studies
      - Summary Clinical Pharmacology [new]
    - m2-7-3-summary-of-clinical-efficacy [indication: pain]
      - Summary of Clinical Efficacy Pain [new]
    - m2-7-4-summary-of-clinical-safety
      - Summary of Clinical Safety [new]
    - m2-7-5-literature-references
      - References [new]
    - m2-7-6-synopses-of-individual-studies
      - Synopses of Individual Studies [new]

Example ToC for paper accompanying a NeeS, based on printing the mx-toc.pdf files.

m1-toc.pdf

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	be - de - package leaflet 10 mg	1.3.1
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	be - fr - intermediate packaging 10 mg	1.3.1
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	be - fr - package leaflet 10 mg	1.3.1
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