

Electronic Submissions in Europe – eCTD and non- eCTD Submissions (NeeS)

January 20, 2009

Objectives

- ◆ Requirements and concepts of the eCTD
- ◆ Overview of types of European filing procedures
- ◆ Implication of filing procedure on the eCTD
- ◆ EU eCTD Module 1 Specifications, v 1.3

Overview

- ◆ eCTD Concepts and Requirements
- ◆ European Filing Procedures: Centralised, Mutual Recognition, Decentralised and National
- ◆ Impact of Filing Procedure on eCTD and NeeS
- ◆ EU eCTD Module 1 Specifications, v 1.3
- ◆ Wrap-up
- ◆ Q&A

Overview of CTD

- ◆ CTD guidelines relate to the ORGANIZATION of the content
 - Do not influence the type of information to include in each section
- ◆ CTD format is required for European Marketing Applications
 - July 1, 2003

Overview of CTD

◆ CTD format based on Modules

- ◆ Module 1: Regional information
- ◆ Module 2: Summaries of information presented in Modules 3 – 5
- ◆ Module 3, Quality: Information related to Chemistry, Manufacturing, and Controls
- ◆ Module 4, Safety: Preclinical study reports and literature references cited in Module 2 Summaries
- ◆ Module 5, Efficacy: Clinical study reports and literature references cited in Module 2 Summaries

Understanding eCTD Concepts and Requirements

- ◆ eCTD composed of two types of specifications
 - Technical Specifications
 - Content Specifications (CTD guidelines)
- ◆ Technical specifications defined in ICH and regional guidance documents
 - ICH eCTD Specification v 3.2
 - EU Module 1 Specification v 1.3
 - ◆ Effective January 1, 2009

Understanding eCTD Concepts and Requirements

- http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol2_en.htm#2a
- <http://esubmission.emea.europa.eu/index.htm>
- <http://estri.ich.org/>

Understanding eCTD Concepts and Requirements

- ◆ Technical Specifications define electronic requirements
 - Required folder and file names
 - Submission metadata
 - XML backbone components
 - Accepted file formats
 - Accepted type of electronic media

Understanding eCTD Concepts and Requirements

- ◆ Technical Validation of Electronic Submissions
 - Virus check at National Competent Authority (NCA) and EMEA
 - Compliance with general requirements
 - Compliance with eCTD structure templates and naming convention
 - Security settings or password protection

Understanding eCTD Concepts and Requirements

◆ Lifecycle Management

- New perspective on submission lifecycle management
- Submission lifecycle starts with original application
 - ◆ Variations
 - ◆ Annual Reports
 - ◆ Supplements
 - ◆ Withdrawals

Understanding eCTD Concepts and Requirements

New: Original or the file has no relationship with files submitted previously

Replace: This new file replaces an existing file

**eCTD File
Operation
Attributes**

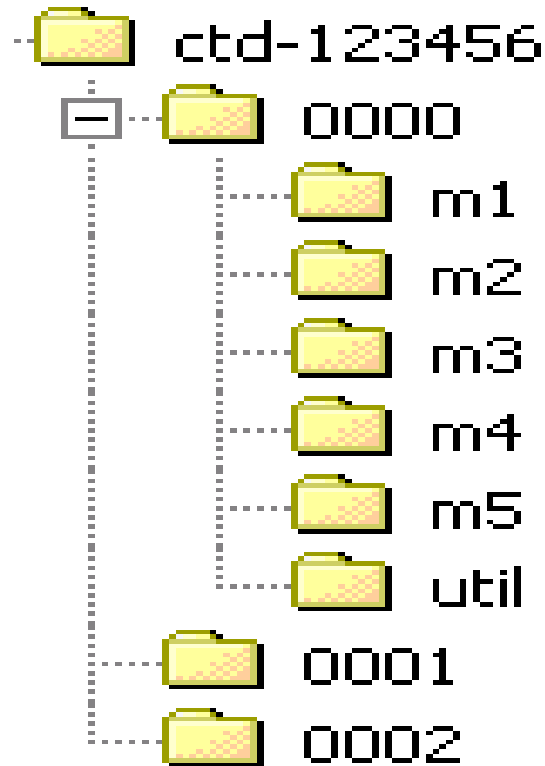
Append: This new file should be associated with an existing file (Not Recommended)

Delete: No new file submitted in this case. Modified file attribute identifies file previously submitted.

Understanding eCTD Concepts and Requirements

- ◆ Lifecycle Management (continued)
 - Critical for document authors to understand use of operation attributes
 - Critical to identify appropriate operation attribute for subsequent submissions
 - Critical to include proper information for modified file when using “Replace”, Append” or “Delete” attributes
 - ◆ Identify proper sequence number

Understanding eCTD Concepts and Requirements



European Filing Procedures

◆ Centralised Procedure

- European Medicines Agency (EMA)
- Member States
- A marketing authorisation granted under the centralised procedure means the medicinal product may be put on the market in all Member States
- Regulations determine if required or optional
- Mandatory eCTD format for electronic-only submissions effective January 1, 2010

European Filing Procedures

- ◆ Mutual Recognition Procedure (MRP)
 - Use if application will be made to several member states and product has received marketing authorization in any member state at time of application
 - Reference Member State (RMS)
 - Concerned Member State (CMS)
 - Repeat Use Procedure (RUP) – use if submitting to a CMS identified after the initial filing

European Filing Procedures

◆ Decentralised Procedure (DCP)

- Use if application will be made to several member states and product has not received marketing authorization in any member state at time of application
- Reference Member State (RMS)
- Concerned Member State (CMS)
- Repeat Use Procedure (RUP)

European Filing Procedures

- ◆ National Procedure
 - Filing application in single member state

Impact of Filing Procedure

◆ Centralised Procedure

- July 2008: EMEA accepts electronic-only submissions with no paper copy of Modules 1 and 2
- January 2009: All Member States accept electronic-only submissions
- January 2009: EU eCTD Module 1 v 1.3 required for all eCTD submissions
- July 2009: eCTD format **STRONGLY** recommended for electronic-only submissions
- January 2010: eCTD **MANDATORY** format for all electronic-only submissions to NCAs

Impact of Filing Procedure

◆ MRP/DCP and National Procedures

- Requirements vary by NCA⁽¹⁾
 - ◆ Electronic: Modules 1 – 5, no paper
 - ◆ Electronic: Modules 1 – 5, paper copy of Module 1
 - ◆ Electronic: Modules 1 – 5, paper copy of Modules 1 - 2
 - ◆ Electronic: Modules 1 – 5, paper copy of Modules 1 – 3
 - ◆ Response Documents
- Reference document: CMD(h) Best Practice Guide on the Use of the eCTD in the MRP and DCP

(1) Source: CMDh Requirements on Electronic Submissions for New Applications within MRP, CDP or National Procedures, Final, February 2008

Type of Electronic Submission

- ◆ Two Types of Electronic Submissions are Accepted
 - eCTD
 - Non-eCTD Electronic Submission (NeeS)
- ◆ NeeS only accepted until January 1, 2010
 - All Member States

Type of Electronic Submission

◆ eCTD vs NeeS

- Same required file formats
 - ◆ PDF, RTF – text documents
 - ◆ JPEG, GIF - images
- Content structured according to CTD requirements
- Folder and files names follow eCTD specifications
- Follow eCTD granularity
- Accepted media types: CD-ROM, CD-R, DVD-R

Type of Electronic Submission

- ◆ Which format to choose is based on filing procedure and Member State(s)
 - RMS and CMS may or may not be able to accept eCTD
 - Confirm with Member State or RMS which format is preferred

Type of Electronic Submission

Module 3	3.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD		
	3.2	3.2.S	3.2.S.1	3.2.S.1.1
				3.2.S.1.2
				3.2.S.1.3
			3.2.S.2	3.2.S.2.1
				3.2.S.2.2
				3.2.S.2.3
				3.2.S.2.4
				3.2.S.2.5
				3.2.S.2.6
			3.2.S.3	3.2.S.3.1
				3.2.S.3.2
			3.2.S.4	3.2.S.4.1
				3.2.S.4.2
				3.2.S.4.3
				3.2.S.4.4
				3.2.S.4.5
			3.2.S.5	
			3.2.S.6	
			3.2.S.7	3.2.S.7.1
3.2.S.7.2				
3.2.S.7.3				

where:

yellow = documents rolled up to this level are not considered appropriate

green = one or multiple documents can be submitted at this level

Type of Electronic Submission

◆ ICH eCTD Specification v 3.2

44	Number	3.2.S.2
	Title	Manufacture (name, manufacturer)
	Element	m3-2-s-2-manufacture
	Directory	m3/32-body-data/32s-drug-sub/substance-1-manufacturer-1/32s2-manuf
45	Comment	
	Number	3.2.S.2.1
	Title	Manufacturer(s) (name, manufacturer)
	Element	m3-2-s-2-1-manufacturer
	File	m3/32-body-data/32s-drug-sub/substance-1-manufacturer-1/32s2-manuf/manufacturer.pdf
46	Comment	For this document there should be only information regarding one manufacturer
	Number	3.2.S.2.2
	Title	Description of Manufacturing Process and Process Controls (name, manufacturer)
	Element	m3-2-s-2-2-description-of-manufacturing-process-and-process-controls
	File	m3/32-body-data/32s-drug-sub/substance-1-manufacturer-1/32s2-manuf/manuf-process-and-controls.pdf
47	Comment	
	Number	3.2.S.2.3
	Title	Control of Materials (name, manufacturer)
	Element	m3-2-s-2-3-control-of-materials
	File	m3/32-body-data/32s-drug-sub/substance-1-manufacturer-1/32s2-manuf/control-of-materials.pdf
48	Comment	The applicant has the option to submit one or multiple files, one for each material
	Number	3.2.S.2.4
	Title	Controls of Critical Steps and Intermediates (name, manufacturer)
	Element	m3-2-s-2-4-controls-of-critical-steps-and-intermediates
	File	m3/32-body-data/32s-drug-sub/substance-1-manufacturer-1/32s2-manuf/control-critical-steps.pdf
49	Comment	The applicant has the option to submit one or multiple files, one for each step
	Number	3.2.S.2.5
	Title	Process Validation and/or Evaluation (name, manufacturer)
	Element	m3-2-s-2-5-process-validation-and-or-evaluation
	File	m3/32-body-data/32s-drug-sub/substance-1-manufacturer-1/32s2-manuf/process-validation.pdf
	Comment	The applicant has the option to submit one or multiple files, one for each validation

Type of Electronic Submission

◆ eCTD vs NeeS

– Primary Difference

- ◆ No XML backbone files are present in NeeS
- ◆ NeeS utilizes PDF Tables of Contents for each individual module plus Comprehensive TOC

Type of Electronic Submission

eCTD Index (XML Backbone)

eCTD DTD version 3.2

- m1-administrative-information-and-prescribing-information
 - [1 Administrative Information and Product Labeling](#) [new]
- m2-common-technical-document-summaries
 - m2-3-quality-overall-summary
 - m2-3-s-drug-substance [manufacturer: ABC Drug Co.] [substance: Wonder Drug]
 - [2.3.S.1 General Information \(ABC Drug Co. Wonder Drug \)](#) [new]
 - [2.3.S.2 Manufacture \(ABC Drug Co. Wonder Drug \)](#) [new]
 - [2.3.S.3 Characterization \(ABC Drug Co. Wonder Drug \)](#) [new]
 - [2.3.S.4 Control of Drug Substance \(ABC Drug Co. Wonder Drug \)](#) [new]
 - [2.3.S.5 Reference Standards or Materials \(ABC Drug Co. Wonder Drug \)](#) [new]
 - [2.3.S.6 Container Closure Systems \(ABC Drug Co. Wonder Drug \)](#) [new]
 - [2.3.S.7 Stability \(ABC Drug Co. Wonder Drug \)](#) [new]

Type of Electronic Submission

Nees Example Comprehensive TOC: Module 3 Quality

Company Name →
Drug name →
Type of Application ¶
XXX.____,SN-0000 ←
Month-Year ¶

- ¶
- **MODULE 3: → QUALITY ¶**
- 3.1 → TABLE OF CONTENTS FOR MODULE 3 [BLUE |
TEXT TO INDICATE HYPERLINK] ¶**
- 3.2 → BODY OF DATA ¶**
- 3.2.S → Drug Substance [DS Name, DS Manufacturer] ¶**
- 3.2.S.1 → General Information [DS Name, DS Manufacturer] ¶**
 - 3.2.S.1.1 → Nomenclature [DS Name, DS Manufacturer] ¶*
 - 3.2.S.1.2 → Structure [DS Name, DS Manufacturer] ¶*
 - 3.2.S.1.3 → General Properties [DS Name, DS
Manufacturer] ¶*

Type of Electronic Submission

– Recent Experience:

- ◆ MAA filed with Medicines Evaluation Board (MEB), Netherlands: requested eCTD format
 - Two applications; different dosage strengths
 - Completed application for one strength first; second application completed within 7 business days
- ◆ Active Substance Master File (ASMF) submitted to Medicines and Healthcare products Regulatory Agency (MHRA) UK: requested electronic copy only (NeeS)
- ◆ ASMF submitted to member states: requested electronic copy (NeeS) and paper copy

Type of Electronic Submission

- Recent Experience:
 - ◆ Sponsor submitting in Europe; primary country not identified; license partner not identified
 - Preparing in NeeS format to allow for greatest flexibility
 - Provide to third party to add appropriate Module 1 information
 - Able to submit electronically or print hard copy
 - Easily converted to eCTD format

EU eCTD Module 1 Specifications

- ◆ EU eCTD Module 1 Specifications, v 1.3
 - Mandatory guideline effective January 1, 2009
 - Primary difference from previous versions was addition of section 1.10 for Paediatric Requirements
 - Also incorporated items from submitted change requests
 - Provides technical specifications for region-specific administrative and product information

EU eCTD Module 1 Specifications

– Accepted File Formats

Table 1 Acceptable file formats for Module 1

Document	File Format	Remark
Cover letter	XML*, PDF, RTF	PDF preferably generated from electronic source.
Administrative forms: <ul style="list-style-type: none"> • Application form and its annexes • Variation application form incl. background for the variation • Renewal form and its annexes 	XML*, PDF, RTF XML*, PDF, RTF XML*, PDF, RTF	Documents should be generated from electronic source documents, any signature may be embedded as a graphic file in the PDF text if desired, although this is not necessary as the hard paper copy contains the legally binding signature.
Product Information: <ul style="list-style-type: none"> • Product information text** • Packaging mock-ups • Reference to specimens 	ZIP, TGZ, PDF, RTF PDF PDF	Labelling texts can be submitted in ZIP or TGZ format according to the PIM Data Exchange Standard. In that context, images can be transmitted in JPEG, GIF, PNG, TIF, SVG, or MathML and PIM information is exchanged in XML. If a higher resolution is necessary for the mock-ups, use JPEG, GIF, PNG or SVG on a case-by-case basis.
Other	PDF, RTF	PDF preferably generated from electronic source.

* = In line with the general principles of the ICH eCTD Specification, it is intended that XML will eventually become the sole submission format for administrative forms and product information documents (as they contain structured data and a long-term goal of this development is the normalisation of data in Module 1). Note that as XML documents become available for practical implementation (including documents other than the above), they will be introduced into Module 1 and the current file formats may ultimately be replaced (after an appropriate transition period)

** = SmPC. Package Leaflet and labelling

EU eCTD Module 1 Specifications

- Directory/File Structure
 - ◆ Specifies when and where individual country codes should be provided
 - Appendix 2.1: Country Codes
 - ◆ Specifies when and where language codes should be provided
 - Appendix 2.2: Language Codes
 - ◆ Specifies SPC, Labelling and Package Leaflet File Name Identifiers (SPCDOC)
 - Appendix 2.3: SPC, Labelling and Package Leaflet File Name Identifiers

EU eCTD Module 1 Specifications

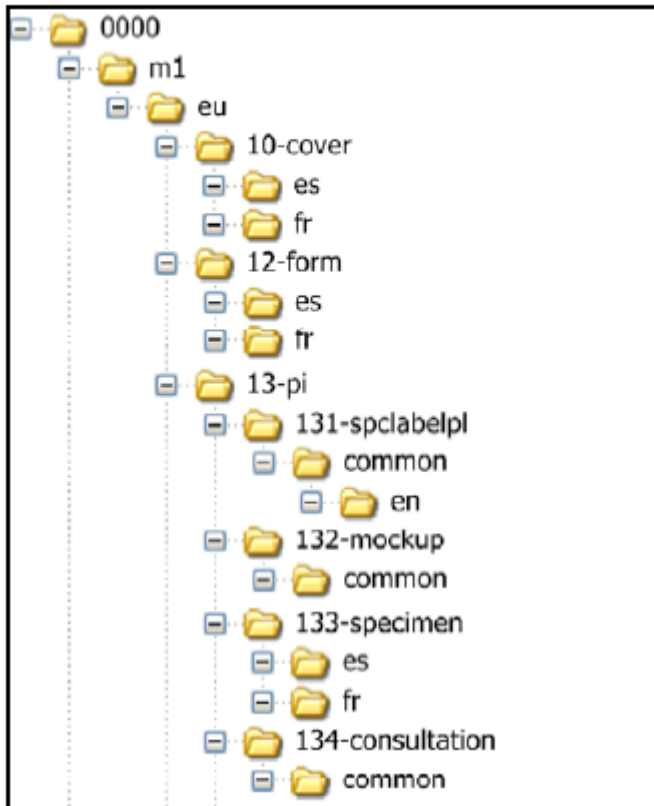
- Appendix 2.4: Agency Codes and Names
 - ◆ Listing of EU Countries, the Agency Code, Human/Vet, and Agency Name
 - Use Agency Code within EU Module 1 XML file

EU eCTD Module 1 Specifications

- ◆ Additional appendices provide examples of directory structure for different filing procedures
 - Also provides examples of XML coding for different filing procedures
- ◆ Choice of filing procedure has greatest impact on Module 1 configuration
 - Important to communicate filing procedure to group compiling eCTD submission early to minimize rework and ensure Module 1 is configured properly

EU eCTD Module 1 Specifications

MRP Directory Structure

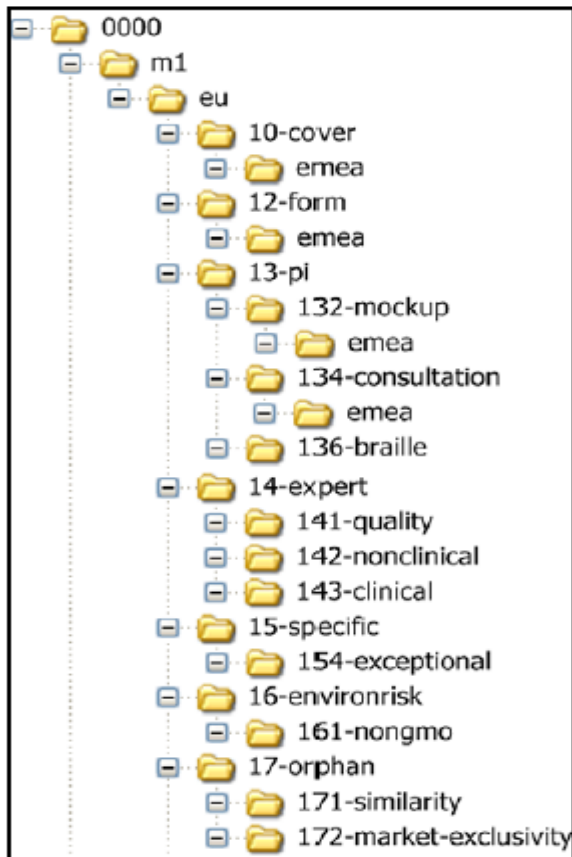


This example is provided with the following options:

- Italy as RMS,
- France and Spain as CMSs,
- submission of PI in PDF,
- generic, hybrid or bio-similar application

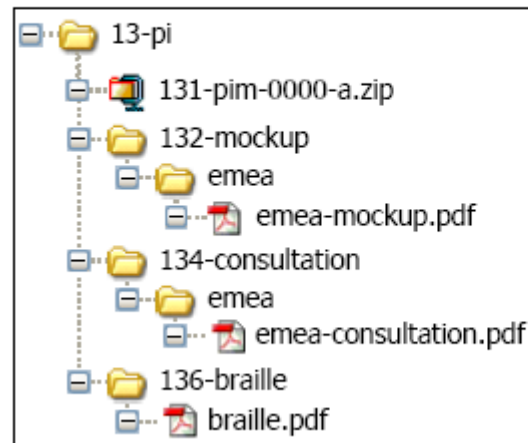
EU eCTD Module 1 Specifications

Centralised Procedure Directory Structure



For the Centralised Procedure, most documents will be in English and valid for all European countries. Files should be placed in the country directories inside the 'emea' directory (for instance cf. directory "10-cover").

Section 1.3 is organised as follows in the context of the submission of product information in PIM format:



Recap of Major Points

- ◆ CTD format mandatory for MAA
- ◆ EU Filing Procedures: Centralised, MRP, DCP, and National
- ◆ Two types of electronic submissions currently accepted:
 - NeeS
 - ◆ Accepted until January 1, 2010
 - eCTD

Recap of Major Points

- ◆ Primary difference between eCTD and NeeS
 - eCTD has XML Backbone (Index) and utilizes lifecycle operation attributes (New, Replace, Append, Delete)
 - NeeS utilizes PDF TOCs for Comprehensive TOC and individual module TOCs

Recap of Major Points

- ◆ Choice of filing procedure impacts type of electronic submission
 - Centralised Procedure
 - ◆ July 2008: EMEA accepts electronic-only submissions with no paper copy of Modules 1 and 2
 - ◆ January 2009: All Member States accept electronic-only submissions
 - ◆ July 2009: eCTD format STRONGLY recommended for electronic-only submissions
 - ◆ January 2010: eCTD MANDATORY format for all electronic-only submissions to NCAs
 - MRP, DCP and National Procedures
 - ◆ Requirements vary by NCA

Recap of Major Points

- ◆ EU eCTD Module 1 Specifications, v 1.3
 - Mandatory guideline effective January 1, 2009 for electronic-only submissions
 - Provides technical specifications and examples of configuration for different filing procedures

Helpful Websites

- http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol2_en.htm#2a
- <http://esubmission.emea.europa.eu/index.htm>
- <http://estri.ich.org/>

Beckloff Associates would be pleased to assist with your eCTDs and NeeSs:

<http://www.cardinalhealth.com/beckloff/>

<http://www.cardinalhealth.com/beckloff/services/publishing/>

<http://www.cardinalhealth.com/beckloff/services/eCTD/>

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