Get ready for eCTD in South Africa

Current status at MCC

E Taute – Feb 2013

Overview

Background

Guidelines, Specifications, Forms

- ICH eCTD Specification V 3.2.2 16-July-2008
- **2.21 South African Specification for eCTD Regional - Module 1**
- **2.22 South African eCTD Validation Criteria**
- **2.23 Guidance for the Submission of Regulatory Information in eCTD Format**
- **2.26 ZA CTD and ZA eCTD Implementation**
- **2.27 eCTD Checksums**
- **6.15 Screening Template for New Applications for Registration**

Process

Background

Why?

Harmonisation

To provide for a common format for the submission of information to the regulatory authorities in the 3 ICH regions + South Africa

- "Common Technical Document" signed-off by ICH in November 2000

Advantages / Objectives:

- Resource saving for industry
- Facilitate simultaneous submission in all the regions
- Facilitate exchange of regulatory information
- Harmonised format to be further supported by the eCTD
- More efficient assessment and navigation, e.g. use of hyperlinks and bookmarks
- Faster availability of new medicines

Background cont.

- 2003 – new format MRF1
- Dec 2003 – PARTs 2 & 3
- EDMS – started 2006
- CTD – location of regional data
  - compulsory June 2011
- Now eCTD

International Conference on Harmonisation (ICH)

Definition of eCTD

- *< The eCTD is defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission.>*
- The content is based on the CTD format, which was defined by the ICH
- *<The eCTD specification lists the criteria that will make an electronic submission technically valid. The focus of the specification is to provide the ability to transfer the registration application electronically from industry to a regulatory authority.>*
- *<Industry to industry and agency to agency transfer is not addressed.>*

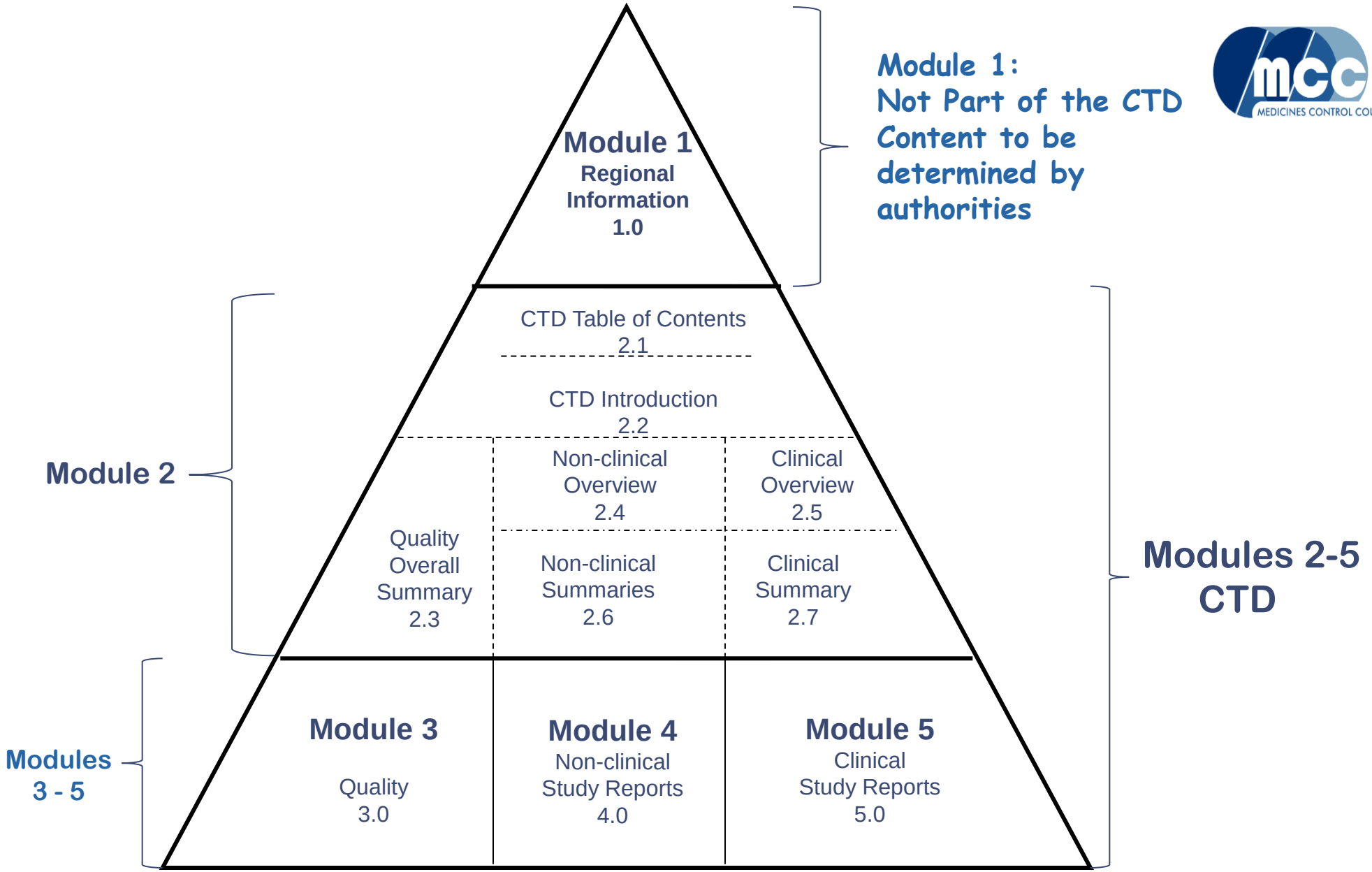
CTD / eCTD

Remember, CTD is only a FORMAT !

It's not a "single" dossier, with a "single" content since

- Legal requirements differ in the regions
- ICH guidelines have not yet harmonised all requirements
- SA guidelines not all harmonised
- Pharmacopoeiae are not harmonised

Is eCTD just electronic CTD?



eCTD – CTD + XML backbone, envelope, metadata

eCTD specification

Why should there be a specification?

- The specification defines uniform structure of the data as well as uniform metadata and uniform document formats for eSubmissions (see SA Module 1 Specification)
- Easier data exchange between companies and MCC (automated check on technical compliance)
- Allows software vendors to configure existing eCTD tools to create and validate eCTD submissions
- Software independency: Different software tools can be used.
- Applicants are free to choose the software tools that match their requirements best

Data management with eCTD submissions:

- eCTD data objects (eCTD sequences) are permanently stored on a file server – the eCTD Repository.
- The metadata (XML backbone) are integrated into the database of the Review system
- The structure and the metadata are displayed in the review tool, where additional data for/of reviewers are added to the eCTD sequence.

eCTD characteristics

Navigation is done electronically

- XML represents the Table of Contents
- Bookmarks guide through documents
- Hyperlinks connect documents in different sections / modules / sequences / submissions

Xml backbone

- Defines the overall structure of the submission
- It has two purposes:
  - Manages metadata for the entire submission and each document within the submission
  - Constitutes a table of contents
- In each sequence there are two « xml backbones »: one for module 1 and one for modules 2 to 5 with links between both
- The « xml backbone » in the eCTD corresponds to the Table of contents (ToC) in the CTD
- The xml file is a small database with all information necessary to play the role of a table of contents

Documents

Paper submission:

- One document is defined as a set of pages numbered from1 to n and divided from the following document by a tab divider

eCTD:

- one document = one file
- Usually PDF format – defined in the specification
- Documents are created from “source documents”, e.g. MS Word files
- Have hyperlinks
- Are paginated from 1 to n
- May have own table of contents (ToC)
- Include bookmarks which should reflect the ToC

Granularity (breakdown of information)

- "… determines the smallest piece of information that is reusable."
- "… defines how the completed document is broken down, tagged, and stored for reuse."
- FDA - Guidance for Industry:

  "Do take advantage of granularity. Don't combine multiple documents into a single PDF

  Think of the future … each document should be provided as a separate file."
- The information contained in one module is not contained in one single document but in several documents => the information is divided
- Recommended granularity – one document per lowest granularity

Granularity……

- In eCTD a new file starts at the same point as in a paper submission, a tab divides the documents
- The granularity of the paper and electronic submissions should be equivalent
- Consider the Life Cycle Management i.e. the replacement of documents / files to be provided when information is changed
- Higher granularity ⇨ smaller files and more files

eCTD Technical requirements

- SA Module 1 Specification for regional requirements
  - differ from country/ region to region
- ICH eCTD specification for international requirements for Modules 2 to 5
  - http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf
- SA validation criteria
  - define rules that are applied to test the eCTD submission for technical compliance with SA Module 1 and ICH eCTD specifications
    - pass or fail, best practice

Guidance for the Submission of Regulatory Information in eCTD Format

- **Practical; business rules**
- **Definitions, e.g.**
  - **Regulatory activity**

➢ A regulatory activity is a logical entity of submission activity (for example a new indication) with a defined start and end point (e.g. initial submission to final approval). In the eCTD world, a regulatory activity consists of all the eCTD Sequences that together make up the life cycle of that particular regulatory activity.

➢ It can also be defined as a collection of **sequences** covering the start to the end of a specific business process, e.g. an initial application for registration or a type C amendment. It is a concept used to group together several business related sequences.

Guidance continued

- **Types of products**
  - ➢ Human medicines – pharmaceutical and biological
  - ➢ Does not apply to veterinary medicines

- **Types of submissions**
  - Road map
  - Once eCTD always eCTD

- **Submission format**
  - eCTD electronic only, but certain documents in paper format as well (Appendix 3) for legal reasons
  - Remember: Format only – consult all other guidelines for content

Structure and content of submission

- **Structure**
  - It is a “folder hierarchy” to provide a “container” for all documents which will be part of a submission
  - ICH eCTD spec includes the directory structure for modules 2 to 5
  - SA spec (regional) specifies the directory structure for module 1
  - Content of information is the same as for paper-based, but location may differ (e.g. ToC) - graphically displayed by XML viewing tool
- **eCTD identifier**
  - Application number used for top-level directory – unique identifier
  - Process before submission
- **Various folders**
  - Sequence number, Util and DTD, Modules 1 and 2 – 5
- **Module 3.2.R**
- **eCTD envelope**

Guidance continued

Sequences

- Each submission has a sequence number
- A sequence number has 4 « digits » and begins with « 0000 »
- Therefore, the first eCTD submission will have the number « 0000 », the next one « 0001 », then « 0002 », etc.
- Sequences following a given submission may be related to this submission or may be independent
- The related eCTD-sequence number describes the relationship of additional information to the original submission or subsequent submissions. *(App 2 of SA Spec)*

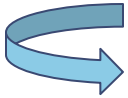
Metadata

- This is « data about data » which are contained in an xml file
- Each **document** contains mandatory metadata (e.g. title, name of the file, sequence, operation attribute)
- Each **dossier** contains mandatory metadata, with information e.g. about the type of submission, the location of the documents, navigation aids

Guidance continued

- **Inclusion of correspondence documentation**

- The term ”correspondence” applies to all communications (documents) that are exchanged between an applicant and the authority in the context of an regulatory activity but which do not have a formal designated placeholder within the eCTD structure.
- Responses to MCC questions are not classified as ‘correspondence’ as the ZA M1 eCTD DTD includes a designated section for such information.
- eCTD exchange is one way only: applicant ⟹ authority



Not all correspondence included, only that directly related to content

e.g. include committee recommendations with letter of application

Guidance continued

- **Letter of Application – folder 1.0 of Module 1**
  - Accompany all submissions - in both paper and portable document format (PDF). The PDF should be a scan of the originally signed document and must be searchable (OCR scanned).
  - State the context of the submission, e.g. the submission type and the application or registration number.
  - The paper and PDF letters must have the same content.
  - Document operation attribute to be “new”.
  - The printout of the checksum file (index-md5.txt) should be attached as an annex to the letter (paper version). The annex must be dated and signed.

Guidance continued

The letter should at least contain the following information:

- Date
- The applicant's name and address
- The proprietary name(s)
- Registration number or Application number
- Dosage form and strength(s)
- The International Non-proprietary Name(s) (INN) of the product
- The submission type
- A description of the submission
- Number of CDs/DVDs provided
- Contact details in case of technical validation issues
- Name and version of eCTD validation tool used to check compliance with the specifications
- The working code as per the General Information guideline

Refer also to the Guidance for the Submission of the South African CTD /eCTD - General & Module 1.

Guidance continued

The following statement must be included:

- "We confirm that the CD/DVD-burning session is closed and the submission is checked with an up-to-date and state-of-the art virus checker: [name of the antivirus software and version of the virus checker]"

- Tabular format of tracking (history) of the submitted sequences (or in annex)
- The letter (paper version) must be signed
- Include / annex eCTD "Reviewer's Guide" or similar document for reviewers if there are specificities concerning the eCTD submission

Technical Requirements

- **Submission media**
  - Hard media e.g. CD / DVD
  - No laptops or other hardware
  - Large application – single DVD rather than multiple CDs
  - Individual modules not split over multiple CDs
  - Adequately packed and labelled
- **PDF files**
  - version 1.4, 1.5, 1.6 or 1.7

Guidance continued

- File naming conventions
- Hyperlinks
- MD5 checksum
- Additional files in MSWord format
  - for the purpose of review and document manipulation
    - M1.2.1, M1.3 (PI, PIL, Label)
- Virus check
  - Positive check will result in refusal of the eCTD
- Validation

MD5 Checksum

- A unique mathematical sum of each byte in a file
- A mechanism to guarantee the integrity of a document and of the whole dossier
- 2.27 eCTD Checksums

za-envelope.mod	**c57b7b7e15f971ece01e1ffcaf4bc459**
za-leaf.mod	**d78dccca9528a2cfcc6301127500ad0b**
za-regional.dtd	**93204dec54a43b911719c1ba3dbaee28**
za-regional.xsl	**dd0f6de92774749ba902a0146480f5c7**

Life Cycle Management

- To know the state of a dossier in comparison with the initial dossier by means of a viewing tool.
- Possible to see all the amendments which were submitted
- Tracking table in Letter of Application:
  - The tracking of the submitted sequences in a tabular format should be included in the letter of application or as an annex to the letter, as per the following example:

Date of submission	Sequence number	Submission type	Related eCTD sequence	Regulatory activity/ Submission description	Regulatory status (submitted / approved / rejected

Operation attributes

- Key to Life Cycle Management (LCM)
- Gives the status of a document in relation to previous submissions and may be:
  - **New** – no relationship with previously submitted documents, e.g. first submission
  - **Replace** – the new file replaces a previously submitted file
  - **Append** - an existing file to which this file should be associated (not recommended)
  - **Delete** – no longer relevant – *not actually deleted*

Validation

2.22 South African eCTD Validation Criteria

Description of Severity		
P/F	Pass / Fail	These are validation criteria that can either be passed or failed. eCTDs that fail to meet one or more of these criteria will be returned to the applicant for fixing and resubmission with the same sequence number.
BP	Best Practice	Any deviation from the criterion should always be reported by the validation tool. It is considered good practice to ensure that these validation criteria are correct in the submitted eCTD. The applicant should make every effort to address these areas before the eCTD is submitted. eCTDs that fail to meet one or more of these criteria will be still be accepted during technical validation. These criteria assess factors that affect the overall ease of use of the eCTD. All tool vendors should include these criteria in their validation tools to enable applicants to produce eCTDs that are easier to use.

Process – what should applicant do?

- Technically correct eCTDs are necessary for a timely and successful review of the submission
- Applicant to check the submission before submitting (to avoid the submission being rejected)

➢Focus: to enable a fully electronic product life cycle

- Once eCTD always eCTD

Process – what should applicant do?

Technical correctness at **document** level:

- This starts with the very first document produced for the eCTD submission
  - e.g. file naming conventions, file formats, document formatting

- Author of document also has responsibility –
  - not only regulatory personnel

Process – what should applicant do?

Technical correctness at **submission** level:

- Ensure technical correctness of the eCTD before submission
- Use validator
- Remember Life Cycle Management – correct use of the LCM operators – new, replace, append, delete)
- Initial submission is first step of LCM – incorrect use may cause problems later in the Life Cycle, e.g. granularity once chosen cannot be easily changed.

IT Tools:

- IT architecture: How to integrate IT tools for eCTD production and publication in the IT environment of the company
- Choosing a product: To comply with the eCTD strategy and the IT strategy e.g. small stand-alone solution vs a more complex but better integrated solution
- eCTD specification defines the entry to the MCC but does not determine the software tool needed
- Applicants are free to choose software tools available that match their requirements

Process at MCC

- Application number before submission
- Administrative check (screening)

A.3 SCREENING / VALIDATION – eCTD

A.3.1 SCREENING (Compliance check)

- Virus check and automated technical validation (verification of technical correctness, compliance with SA validation criteria)

A.3.2 TECHNICAL VALIDATION

- Upload to file server (storage of the original eCTD sequences (data and documents), not modifiable

A.3.3 BUSINESS VALIDATION (Content check)

- Review system – content validation

Process - Implementation

Phased implementation

1: New applications for registration - Limited number of applications to allow for testing of processes
   - Then go live with new applications for registration

2: Amendments – to decide on the type for which a baseline submission should be considered

3: Other

- Optimise guidelines and specifications as experienced is gained in pilot phase and after going live

The road ahead

- Paradigm shift
- Major changes in submitting and processing of applications
- New skills because of new tasks for regulatory personnel in industry and at MCC - training
- New skills for evaluators – training
  - When more skilled in use of the review tool, can spend more time on content
  - eCTD one-way – still paper transmission from MCC to applicant

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