Introduction of eCTD in South Africa

SAPRAA

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Overview

eCTD

- Specifications, Guidelines
  - Guidance and Technical requirements
- Implementation
- Pilot project
  - Technical validation failure
  - Business validation failure
- The road ahead

eCTD specifications

- ICH eCTD Specification V 3.2.2 16-July-2008 for international requirements for Modules 2 to 5
  - http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf
- Regional (Module 1) and validation
  - Based on Swissmedic
- 2.21 South African Specification for eCTD Regional - Module 1
- 2.22 South African eCTD 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
- 2.27 eCTD Checksums

eCTD guidance

- Also based on Swissmedic
- 2.23 Guidance for the Submission of Regulatory Information in eCTD Format
  - 2.24 Guidance for the submission of the South African CTD / eCTD – General & Module 1
- 6.15 Screening Template for New Applications for Registration
  - Includes validation of eCTD
- 2.26 ZA CTD and ZA eCTD Implementation
- Q&A document

eCTD guidance *cont*.

Structure and content of submission

- **Structure**
  - 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 for allocation of number
- **Various folders**
  - Sequence number, Util and DTD, Modules 1 and 2 – 5
- **Module 3.2.R**
- **eCTD envelope**

eCTD guidance *cont*.

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**.

eCTD guidance
Letter of application *cont*.

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

eCTD 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

eCTD technical requirements *cont*.

Life Cycle Management

- 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, e.g.:

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

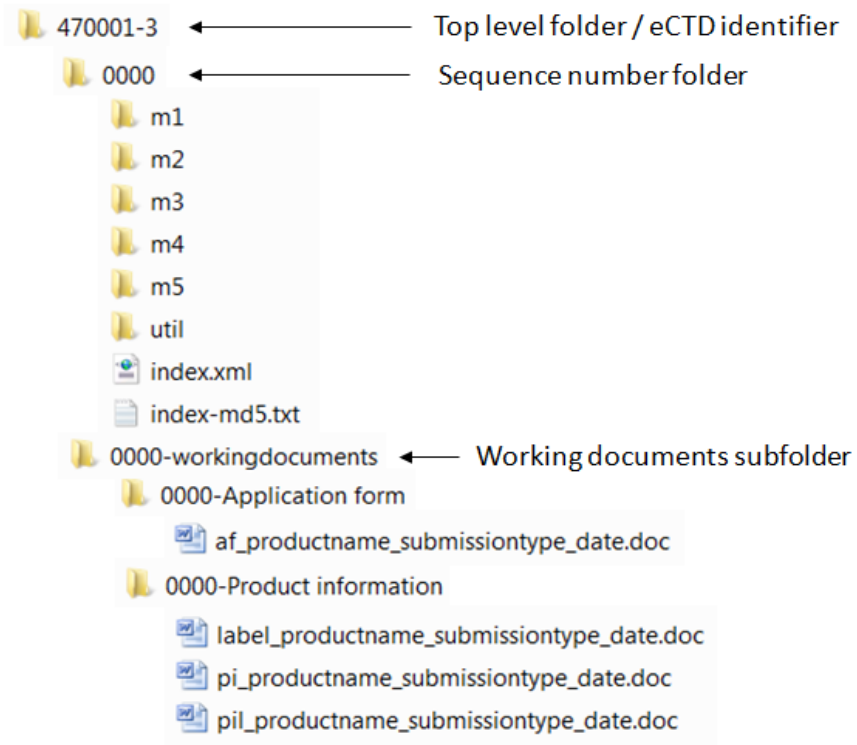
4.7 Additional files in Word format.

MCC requires Word documents for the following documents, in addition to the PDF for the purposes of review and document manipulation:

- Module 1.2.1 Application form
- Module 1.3:
  - Package insert
  - Patient Information Leaflet
  - Label

eCTD technical requirements *cont*.

- Word files should be placed on the same data carrier, alongside the 0000 (or appropriate) eCTD sequence, not within it



eCTD technical requirements *cont*.

List of documents requested additionally in paper format

Module No	Name of document
1.0	Letter of Application
1.2.1	Application form
1.2.2.1	Original cheque or proof of payment with copy of letter of application in a separate envelope
1.2.2.4	Electronic copy declaration
1.5.2.2.2	Original or certified copy of registration certificate, where relevant
1.5.2.3	Affidavit by Responsible Pharmacist
1.8	Screening template
N/A	MD5 checksum
N/A	Technical Validation Report and, if relevant, justification for any Best Practice criteria that are not met

eCTD technical requirements *cont*.

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 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

eCTD 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 experience is gained in pilot phase and after going live

eCTD implementation

ZA CTD	Voluntary / recommended	Implementation date
New product applications for registration	I July 2010	1 June2011
Post-registration amendments Type A, B and C	1 October 2010	1 June2011
ZA eCTD	**Date**	
Pilot phase - new applications for registration		
Step 1: Identify applicants and applications	*1 March – 31 May 2012*	
Step 2: Run pilot phase	*1st June – 28 Feb 2014*	
Maintenance phase		
Step 3: Start maintenance phase	*1 March 2014*	
Start Operational Phase		
Step 4: eCTD process open to entire industry for new applications for registration	*1 June 2014*	
MRF1 format	**Last date for acceptance**	
New product application for registration	31 May 2011	
Clinical evaluations	31 May2011	
Post-registration amendments Type A, B and C	31 May 2011	
Post-registration amendments Type A, B and C*are not acceptable in MBR1 format**		
Conversion of all other MBR1 and MRF1 dossiers	1 June2016	

Pilot project

Products

- 18 Applicants
- 18 products ➡ 42 products because of different strengths: 480399 - 480441
- 9 NCEs of which 3 biologicals
- 9 Generics (multisource)

Reviewers

- 8 Experienced external + 2 internal
  - 3 clinical, 4 quality, 1 biological
  - 1 Names & Scheduling, 1 Inspectorate
- Computer infrastructure
- Off-line projects
  - Distribution & retrieval of submissions

Pilot project *cont.*

- Only 2 submissions passed technical & business validation upon first submission
- 4 submissions failed technical validation
- 12 submissions passed technical but failed business validation
- Up to 4 sequences before complying
- New sequence 0000 instead of 0003 to minimise confusion in first review
- Because of invalid sequence 0000, non-compliance in business validation only detected in sequence 0001
- Errors corrected in 0001 only to find new errors, e.g.
  - letter OCR scanned in 0000 but not in 0001
  - Application forms of different strengths identified in 0000 but not in 0001
  - PIL no longer hyperlinked

Electronic not as patient as paper

Validation

GLOBALvalidator		
	Responsible:	Date/Sign:
	mkwanm	25 October 2013
Submission folder:	D:\ \ 0000	
Validation Set:	MCC-eCTD v1.0 (DTD 1.0) eCTD 3.2 with ZA M1 regional part Version: MCC validation criteria v1.0 Last modification date: 22 February 2013	
Validation Comp. / Lib. Version:	2.0.0.0029 / 1.2.22.8	
Check Result:	Invalid	

Summary:

Total files	204
Valid files	201
Valid files with minor issues	0
Invalid files	3
Skipped files	0
Failed submission level tests	1
MD5 Checksum	e124a17d2a9ba0ecf36baaa7fe30cd7f
Validation Start	25 October 2013, 11:21:01
Validation End	25 October 2013, 11:22:35

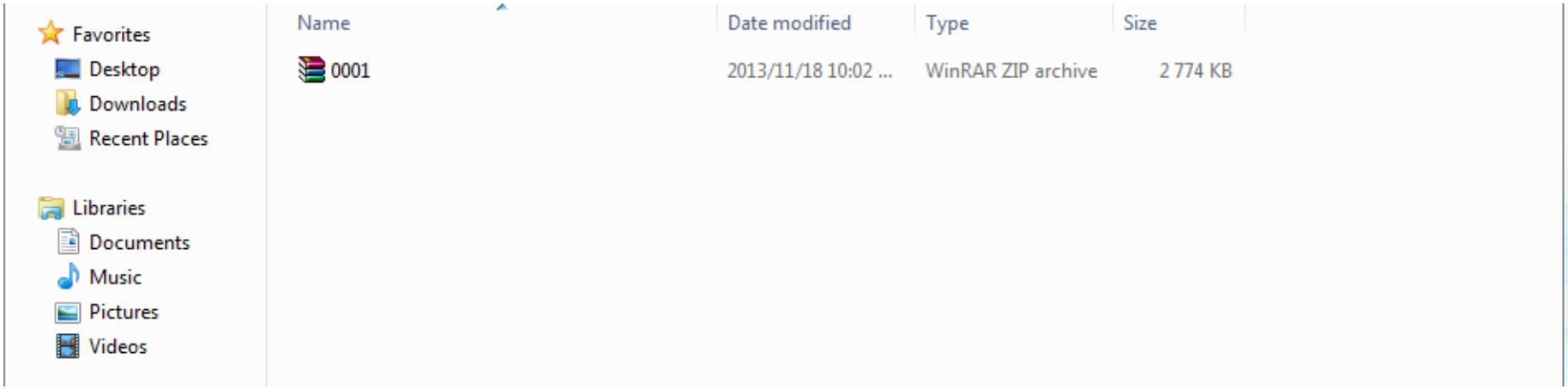
Technical Validation Failure

- All showed own validation = valid
  - Validation carried out on the submission e.g. on desktop and not on medium submitted
- Files in Module 3 found to be missing
  - Export path too long
- Checksum not valid
- PDF protected by security settings or a password (rule no. 18)
- File or folder name contains invalid characters

Technical Validation Failure *cont.*

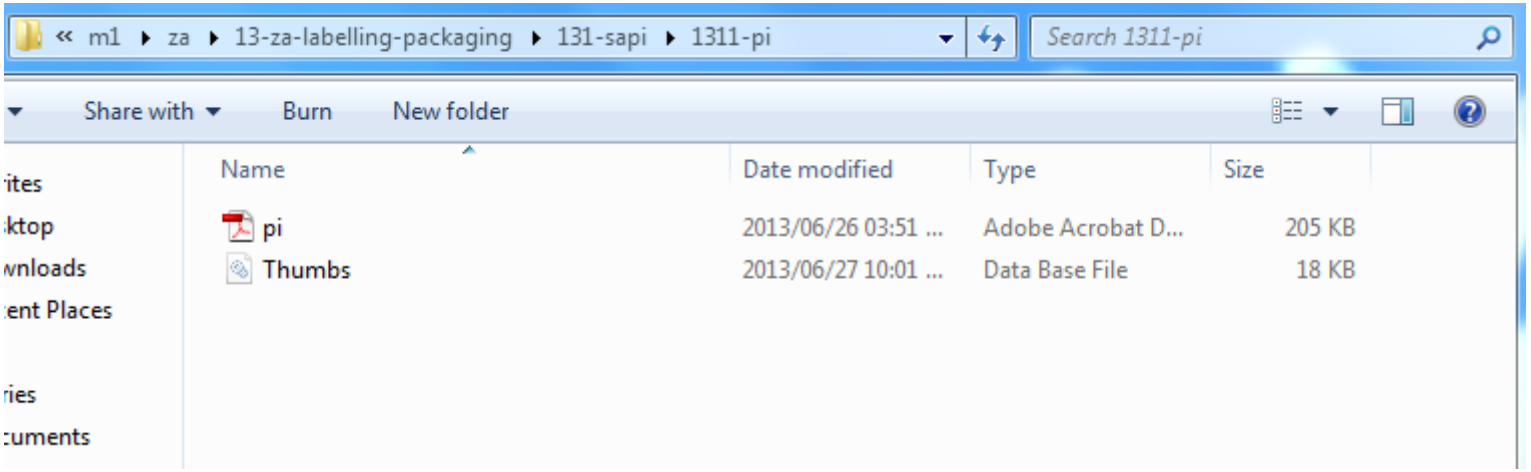
- Unable to make ISO copy
  - DVD-RW or CD-RW used

  - Multisession DVD suggesting that it may not have been properly closed
  - Zipped file submitted



Technical Validation Failure *cont.*

- Unreferenced files



Technical Validation Failure *cont.*

- The thumbs.db files resulting in the error can be prevented. The following link to the Microsoft webpage may be of assistance in this regard:

  http://social.technet.microsoft.com/Forums/windows/en-US/fbc49141-96b3-4350-870a-5b74dcf59c20/how-to-disable-thumbsdb-files-generation-on-network-folders
- Won't see thumbs.db files unless you've checked "Show Hidden Files and Folders" in the Folder Option panel and are using the icon mode in Explorer

Technical Validation Failure *cont.*

- To disable thumbs.db for Windows XP
  - Open My Computer
  - Click on Tools
  - Click Folder Options
  - Click the View tab
  - Put a check in the box next to “Do not cache thumbnails”
  - Click OK

Best Practice Warnings

File size exceeds 100 MB (rule no. 28)

/m3/32-body-data/32p-drug-prod/active-capsuleallstrengths/32p2-pharm-dev		
pharmaceutical-development-ca01-nrp104.pdf		
pharmaceutical-development-ca02-nrp104.pdf		
pharmaceutical-development-ca03-nrp104.pdf		
The file size exceeds 100 MB.	No. 28	Warning
filesize : 128.638 MB		
Hint: Individual files do not exceed 100 MB in size.		
pharmaceutical-development-ca04-nrp104.pdf		
pharmaceutical-development-ca05-nrp104.pdf		
pharmaceutical-development-ca06-nrp104.pdf		
pharmaceutical-development-compatibility.pdf		
pharmaceutical-development-components-drug-product.pdf		
pharmaceutical-development-container-closure-system.pdf		
pharmaceutical-development-drug-product.pdf		
pharmaceutical-development-manuf-proc-development.pdf		
pharmaceutical-development-manuf-process-development.pdf		
pharmaceutical-development-microbiological-attributes.pdf		

Best Practice Warnings *cont.*

- Broken bookmarks
- Broken hyperlinks
- PDF does not open in “Most recent view”

/m1/za/10-application-letter		
application-letter-0001.pdf		
The PDF does not open in 'most recent view'.	No. 38	Warning
0001 : Title: 1.0 Application Letter, Destination:		
wrongzoomcount : 1		
Hint: PDFs open in “most recent view” (i.e. 'inherit zoom' for bookmarks and links, and 'default' in open dialogue box. (ICH eCTD spec p7-4)).		

Business Validation issues

- Incorrect information in envelope
  - Data in support of efficacy
    - Biostudy + Other
    - Clinical + Non-clinical
  - Related sequence

eCTD Sequence:	0001
Related eCTD Sequence:	none
Duplicate Applications: (Proprietary Names / Dates of Application)	N/A / N/A

- Information in envelope ≠ 1.2.1 ≠ 1.8
- Letter not OCR scanned
- Application Form 1.2.1 not OCR scanned

Business Validation *cont.*

- PI / PIL / Labels not hyperlinked
- Screening template not hyperlinked for ease of technical verification by reviewer
- Module 2 not hyperlinked to 3 / 4 / 5

Hyperlinking is crucial to facilitate review of the application

- CDs not correctly labelled
- 1.2.1 not signed
- Confusion of dates in follow up sequences

Business Validation *cont.*

- Official document name in footer of 1.2.1 and 1.8 changed

121 CTD Application form .doc March 2011 page 1 of 7

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*Veterinary applications

Module 1.2.1 Mar11 v3 March 2011 page 1 of 6

1.8 Screening template.docx ***March 2013*** Page 2 of 13

6.15_Screening_template_SA_Feb13_v6.docx *March 2013* Page 1 of 12

Business Validation *cont.*

- Application number not included in 1.2.1
- 3.2.R Regional Information
  - Node extensions not used
  - Section numbers not included
- 3.2 Body of Data
  - Sections included that are not applicable
    - This affects life cycle management of these sections

3.2.R structure

The structure of Module 3.2.R can be graphically displayed by an XML viewing tool. See Figure 4 for an example.

Figure 4

The lack of the required granularity in Module 3.2.R may cause a rejection of the eCTD due to non-compliance with business validation.

Tech validation	Business validation
Valid	Fail
Valid	Fail
Valid	Valid
Valid	Fail
Valid	Valid
some issues	
Valid	Fail
Valid	Valid
Valid	Fail
Valid	Valid

Fail	
Valid	Fail
Valid	Valid
Fail	
Valid	Fail
Valid	Valid
Valid	Fail
Valid	Valid

Fail	
Valid	Fail
Valid	Valid
Valid	Fail
Valid	Fail
Valid	Fail
Valid	Fail
Valid	related 0001
Valid	Valid
Valid	Fail
Valid	Fail
Valid	Fail
Problem	
Valid	Valid
CD dd 2 Aug	
Valid	Valid

Valid	Valid
Valid	Valid
Valid	Fail
Fail	
Valid	Fail
Valid	Fail
Valid	
Valid	Fail
Valid	Fail
Valid	Valid
Valid	Fail
Valid	Valid
Valid	Valid

Valid	Fail
Fail thumbs.db	
Valid	Fail
Valid	
Valid	Fail
Valid	Fail
Valid	

Validation

- MCC is trying to increase acceptance rate by naming the unnecessary errors e.g. missing OCR-scanning

The road ahead

- Paradigm shift
- Major changes in submitting and processing of applications
- IT infrastructure
- 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
- Workshop with industry before going live
- Review of Guidelines & technical requirements