eCTD
Practical experiences of the eCTD pilot project and way forward

26 August 2016

SAPRAA

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Overview

- Pilot Project
- Specifications & Guidelines
- Requirements *vs* Actual
  - Validation issues
  - Lifecycle management
  - Leaf titles
  - Evaluation phase
- Lessons learnt - conclusion
- eCTD roll out

Pilot project

Products

- 18 Applicants
- 18 molecules ⟹ 43 products because of different strengths
  - 9 NCEs of which 3 biologicals
  - 9 Generics (multisource) + 1 duplicate

Reviewers

- 9 Experienced external + 2 internal
  - 3 clinical, 4 quality, 1 biological, 1 scheduling
  - 1 Names & Scheduling, 1 Inspectorate

Pilot project - cont

Status

- 4 products registered
  - 2 NCEs
  - 2 Generics and a duplicate
- 1 product rejected by MCC
- 1 product withdrawn by applicant
- 12 products at various stages
- additional strength included for 1 product in the process

CTD

Guidelines & Specifications

Everything required for paper CTDs

PLUS eCTD specific documents

CTD e.g.:

- ZA CTD
- Module 1.2.1
- 2.01 General Information
- 2.05 Stability
- 2.06 Biostudies
- 2.07 Dissolution
- …..
- 2.24 Guidance General Module 1
- 2.25 P&A CTD
- *6.15 Screening template for new applications for registration*
- SA Guide to GMP

Plus

- *6.16 Validation Template for Applications for Registration in eCTD Format*
- 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
- 2.27 eCTD Checksums
- 2.28 Q&A Implementation of eCTD in South Africa
- Electronic Common Technical Document Specification V3.2.2 (http://estri.ich.org/eCTD/)

eCTD ??

eCTD requirements

2.21 Specification and 2.23 Guidance

- Requirements for copying and pasting, viewing, searching and navigating
- File formats, PDF versions, requirement for OCR scanning
- Maximum individual file size
- Labelling of media
- Letter of application
- Lifecycle management, e.g. For the letter of application leaf elements provided with all eCTD-sequences, the operation attribute should always be "New."
- 3.2R structure

2.22 South African eCTD Validation Criteria

- Pass, fail, and best practices

Requirement vs Actual

Administrative errors

- CDs not correctly labelled
- Validation template (in 1.8) – *hard copy not included*
- MD5 checksum not signed and dated
- Virus check statement in letter does not indicate virus-free
- Amendment schedule attached in hard copy – *not required*

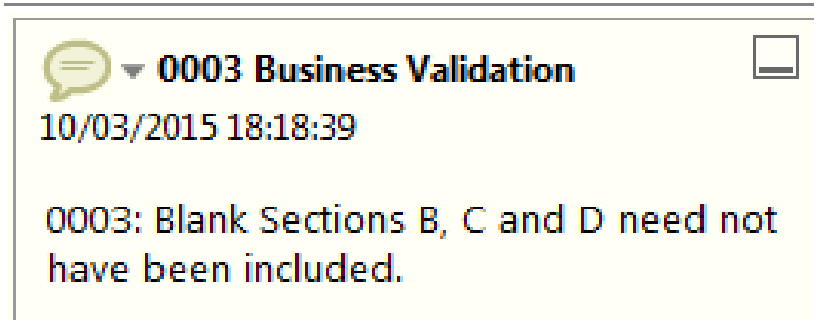
Administrative errors *cont.*

VALIDATION TEMPLATE FOR APPLICATIONS FOR REGISTRATION IN eCTD format

The Validation Template is to be used on receipt of an application for registration of a medicinal product for human use submitted to the South African Regulatory Authority in eCTD format, as well as for follow-up sequences.

Sequence 0000 (new application for registration): Complete Sections A.1, A.3, B, C, and D.

Amendments / follow-up sequences: Complete and submit only Sections A.1, A.3



Administrative errors *cont.*

Validation template

8a	Letter of Application (module 1.0)	C	Y ☐	N ☐	
	• Has the virus check statement been included?	C	Y ☐	N ☐	
	• Does the virus check statement indicate that the submission is virus-free	C	Y ☐	N ☐	
	• Does the letter of application clearly indicate different strengths?	C	Y ☐	N ☐	N/A ☐

Administrative errors *cont.*

Element 1.8 - Validation Template

1 The date of receipt is for this office to complete.

2 The requirement for follow-up sequences was not adhered to. Only sections A.1 and A.3 need be submitted.

3 It should be confirmed in the letter of application that the submission is virus-free - A.1 8a.

Documents in paper format

2.23 Guidance

***Mandatory for all application types**

Module no.	Name of document
*1.0	Letter of Application
*1.2.1	Application form (also for PI amendments)

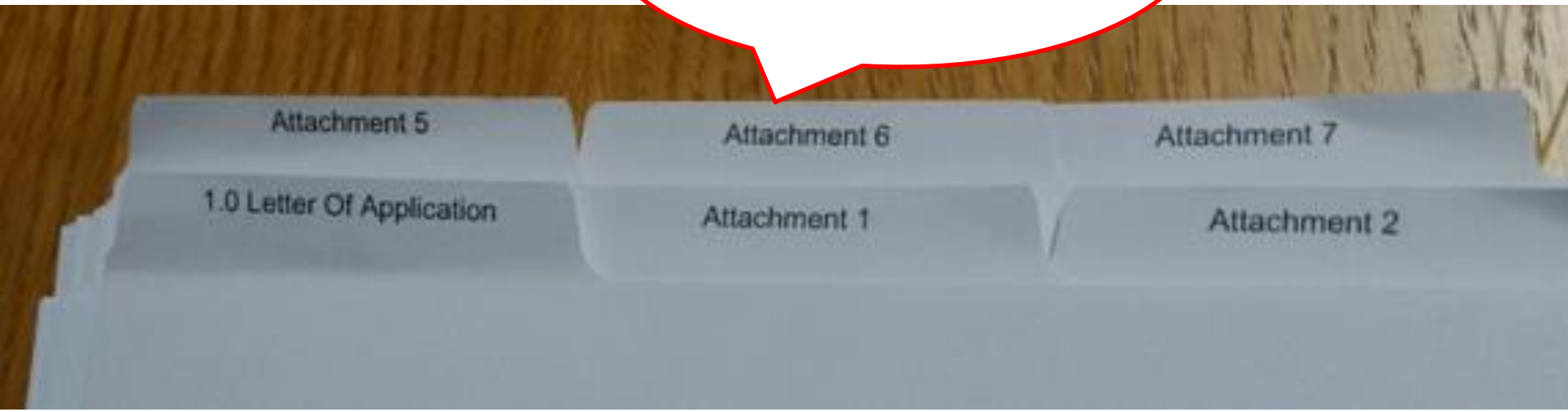
Validation template:

8 Have the following documents in paper format been submitted

	relevant
1.5.2.3	Affidavit by Responsible Pharmacist
*1.8	Screening (Validation) template Section A.1 & 3 only for amendments
N/A	MD5 checksum – annex to letter, dated & signed
N/A	Technical Validation Report and, if relevant, justification of any Best Practice criteria that are not met

Documents in paper format *cont.*

Not module section numbers



Technical Validation

valid

EURS is Yours		
	Responsible:	Date/Sign:
	gessert	28 January 2013
Submission folder:	C:\Users\gessert.EXTEDO\Desktop\MCC \EXTEDIUM-tablets-clin-non-clin\0000	
Validation Set:	MCC-eCTD v1.0 (DTD 1.0) eCTD 3.2 with ZA M1 regional part Version: MCC validation criteria v1.0	
Validation Comp. / Lib. Version:	2.0.0.0016 / 1.2.21.32	
Check Result:	Valid	

Summary:

Total files	67
Valid files	67
Valid files with minor issues	0
Invalid files	0
Skipped files	0
Failed submission level tests	0
MD5 Checksum	1572437509ebec299c23da7867312f33
Validation Start	28 January 2013, 17:15:21
Validation End	28 January 2013, 17:15:22

invalid

EURS is Yours		
	Responsible:	Date/Sign:
	gessert	07 February 2013
Submission folder:	C:\Users\gessert.EXTEDO\Desktop\MCC \EXTEDIUM-tablets-clin-non-clin - invalid\0000	
Validation Set:	MCC-eCTD v1.0 (DTD 1.0) eCTD 3.2 with ZA M1 regional part Version: MCC validation criteria v1.0	
Validation Comp. / Lib. Version:	2.0.0.0016 / 1.2.21.32	
Check Result:	Invalid	

Summary:

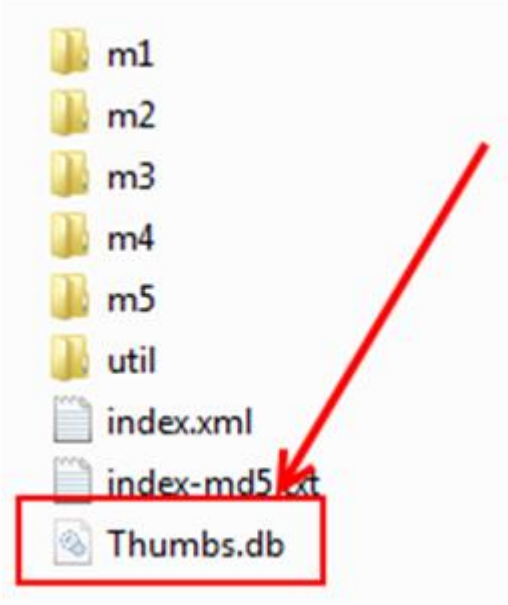
Total files	67
Valid files	65
Valid files with minor issues	0
Invalid files	2
Skipped files	0
Failed submission level tests	1
MD5 Checksum	a8c468c5a403888f89e1c4130b9c9ebdc
Validation Start	07 February 2013, 11:29:13
Validation End	07 February 2013, 11:29:15

Technical Validation failure *cont.*

- File or folder name contains invalid characters
- DTD checksums not valid
- PDF password protected
- Unreferenced files
- Files in Module 3 missing (export path too long)
  - *All showed own validation report as "valid" - but validation carried out on the submission e.g. on desktop and not on medium submitted*

Technical Validation failure *cont.*

- Thumbs.db files
  - Unreferenced files



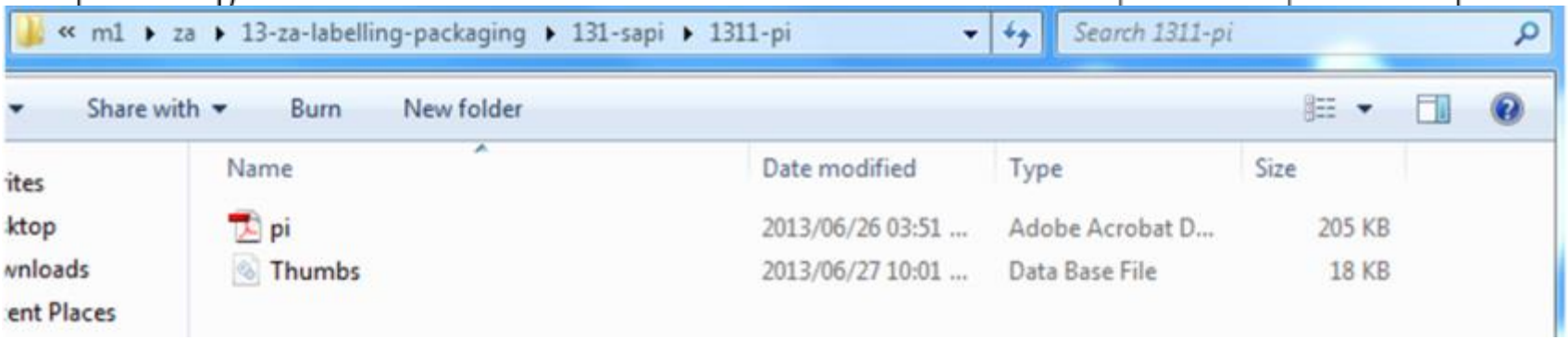
To avoid creating thumbs.db files, the applicant is advised not to open files or folders *after publishing* and *before burning* the sequence on CD.

It is possible to disable thumbs.db files in Microsoft Windows.

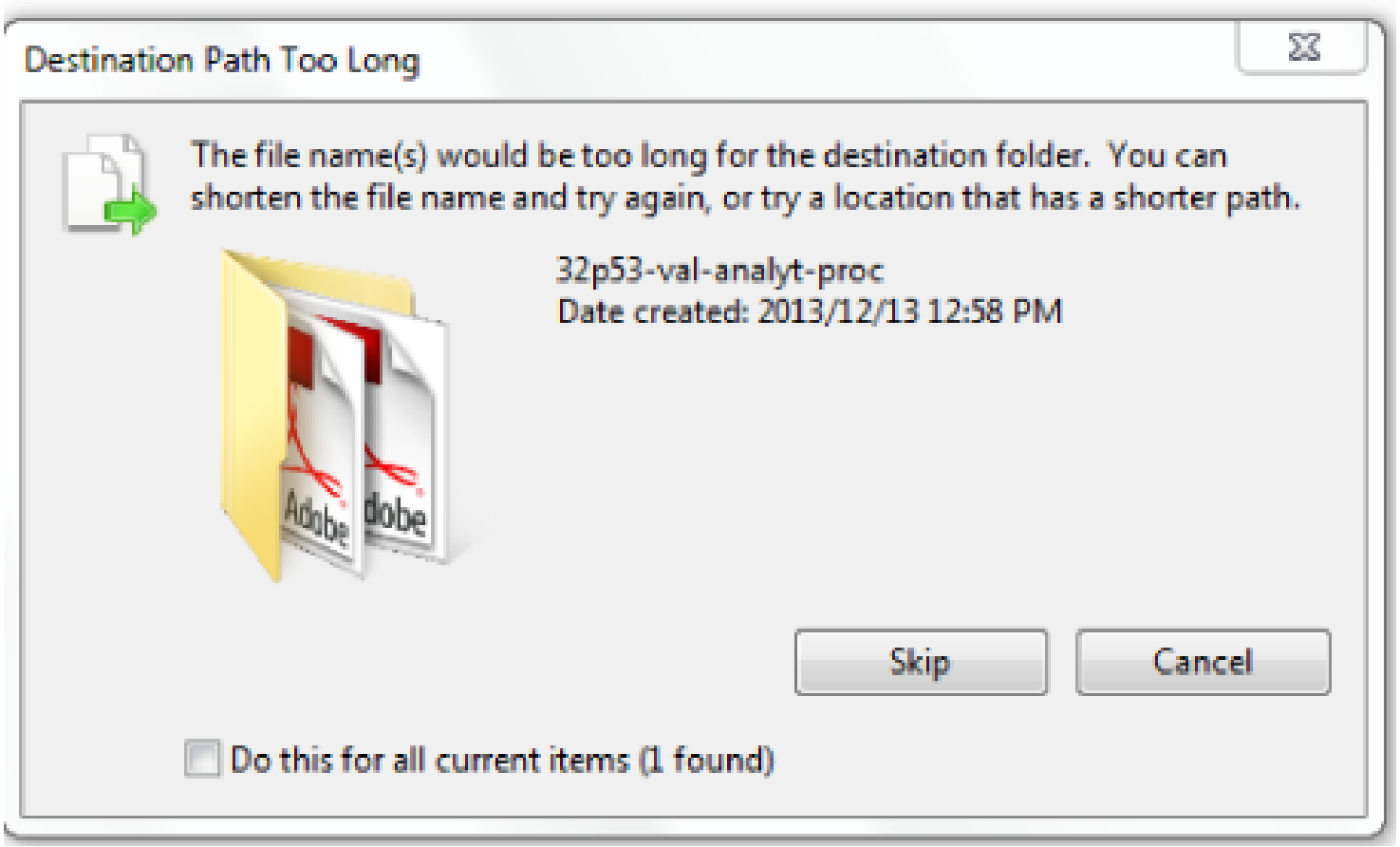
Technical Validation Failure *cont.*

- Unreferenced files

Status	Path/File	Rules	Severity
	(Submission)		
	Submission level tests		
	Unreferenced files found.	No. 07	Error
	d:\ \0000\m3\32-body-data\32r-reg-info\32r1-availability\32r11-overview\thumbs.db :		
	d:\ \0000\m3\32-body-data\32r-reg-info\32r1-availability\32r14-pharmaceuticalavailabilitystudies\32r142-other\thumbs.db :		
	d:\ \0000\m3\32-body-data\32r-reg-info\32r6-animal-human-orig \thumbs.db :		
	Hint: There are no unreferenced files in the root folder, M1, M2, M3, M4 & M5 folders (including subfolders but excluding 'util' subfolders, the index-md5.txt and index.xml).		



Technical Validation failure *cont.*



Technical Validation Failure *cont.*

- Unable to make ISO copy – new and responses
  - DVD-RW or CD-RW used

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

Prevent Technical Validation Failure

- Carry out validation on medium submitted to prevent false valid result. Don't open files or folders *after publishing* and *before burning* the sequence on CD.
- Check export path length – prevent files from not being exported and to be missing
- Checksum to be valid
- PDF not to be protected by security settings or a password *(current rule no. 18)*
- Ensure that file or folder name contains no invalid characters

Best Practice Warnings

File size exceeds 100 MB (rule no. 28)
being changed to 200 MB

/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)).		

Best Practice Warnings *cont.*

Life cycle management

2.23 Submission in eCTD format

Operation attribute to be “new”

1.0 Letter of application

1.2.1 Application form

1.2.2.1 Proof of payment

1.2.2.4 Electronic copy declaration

1.5.2.1 Tabulated schedule of amendment

Validation template

6 For follow-up sequences, is the operation attribute of the following documents reflected as “new”

Business validation failure

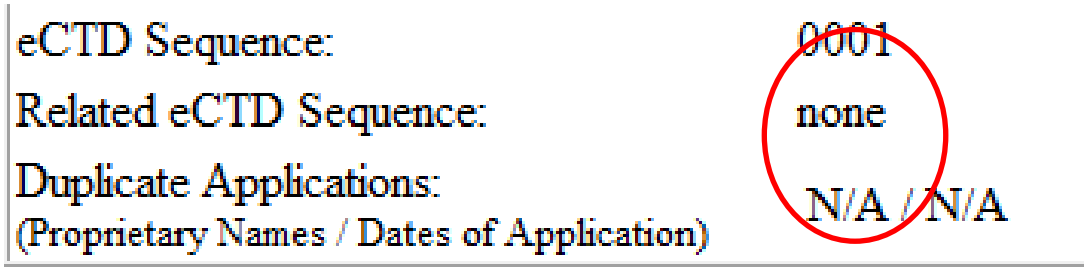
- Incorrect operation attribute (lifecycle)
- PI / PIL / Labels not hyperlinked
- Module 2 not hyperlinked to 3 / 4 / 5
- 3.2.R granularity incorrect
- Letters not OCR scanned
- Application Form 1.2.1
  - not signed, application number not included
  - not OCR scanned
  - follow-up sequence - document operation attribute not **“new”.**
  - Incorrect dates in follow up sequences
- Incomplete or incorrect data in envelope

Business Validation *cont.*

- Validation template not hyperlinked for ease of technical verification by reviewer, and hard copy not included in M1.8
- Official footers of forms changed
- Because of invalid sequence 0000, non-compliance in business validation only detected in replacement sequence
- 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 with leaf titles in 0000 but not in 0001
  - PI/PIL no longer hyperlinked

Business Validation *cont.*

- Incorrect information in envelope
  - Data in support of efficacy incomplete
  - Related sequence



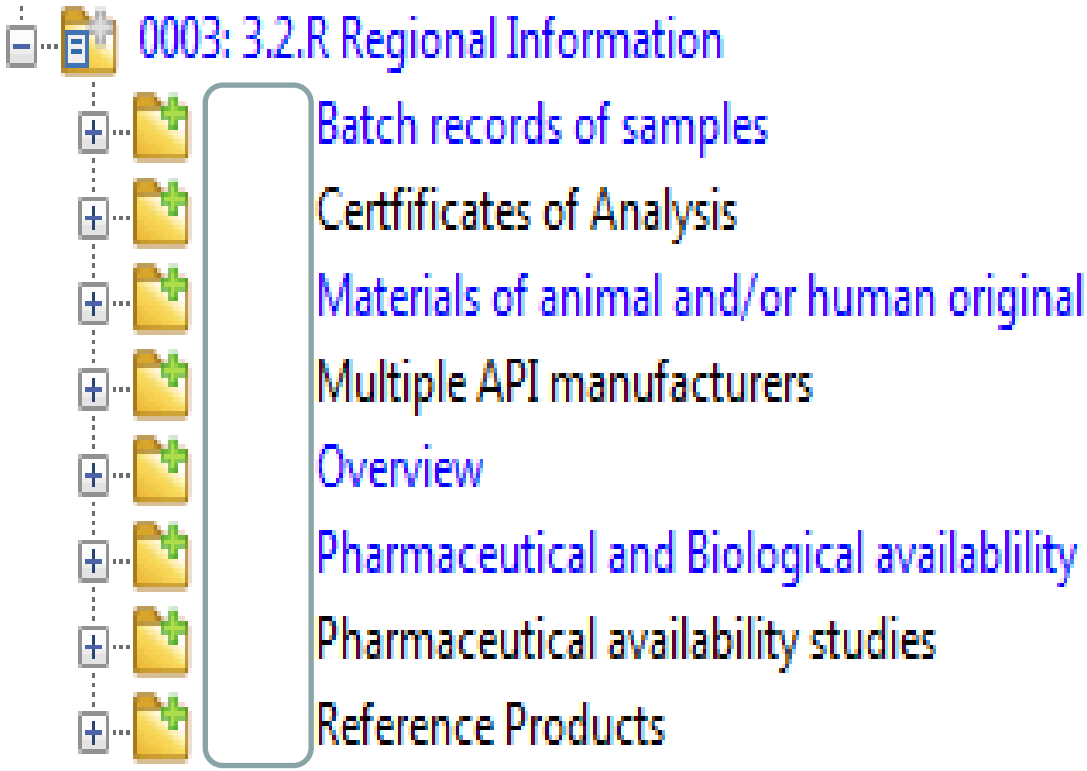
eCTD Sequence:	0001
Related eCTD Sequence:	none
Duplicate Applications: (Proprietary Names / Dates of Application)	N/A / N/A

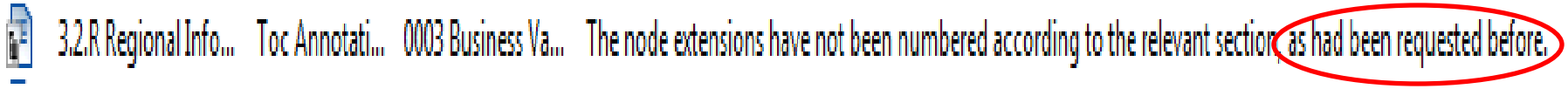
- Information in envelope ≠ 1.2.1 ≠ 1.8

Business Validation *cont.*

- 3.2.R Regional Information
  - Incorrect granularity
  - 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

Business Validation *cont.*





Business Validation *cont.*

Element 1.0 Letter of application

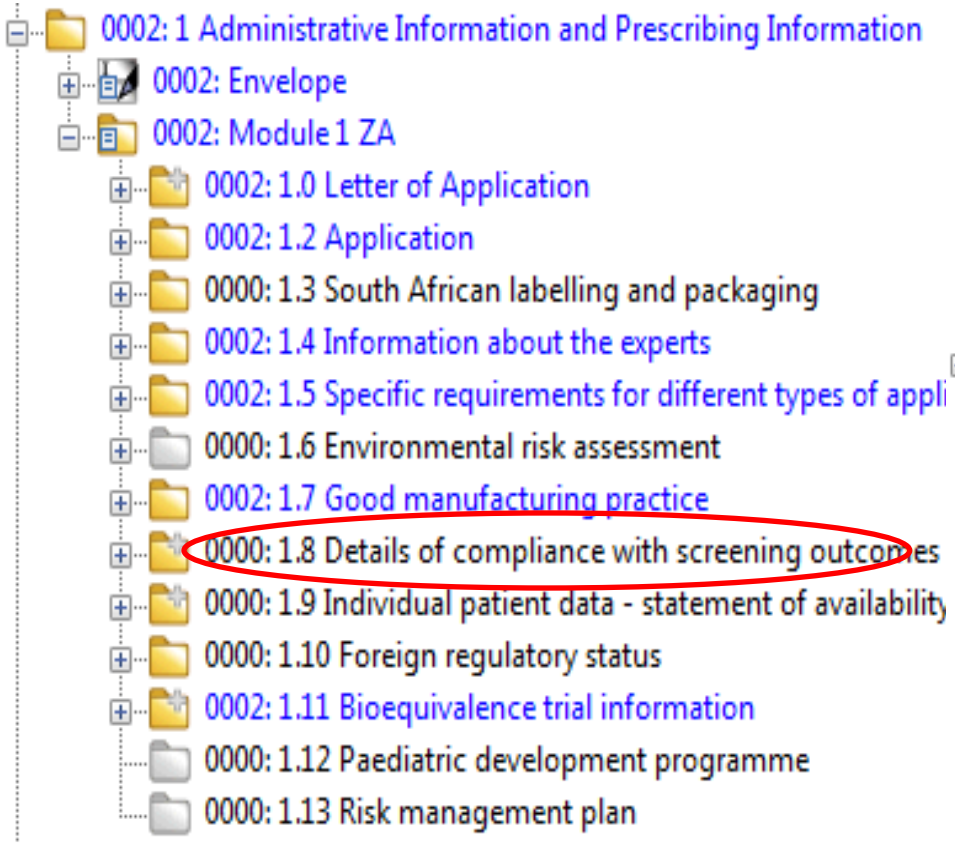
- The amendment schedule should not be an attachment to the letter, but be included in M1.5.2.
- The use of the amendment schedule is not correct:
  - The column for the Reviewer's comment is required.
  - The differences between the current and amended modules have to be indicated.

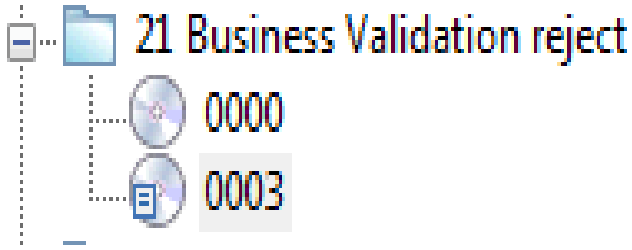
Business Validation *cont.*

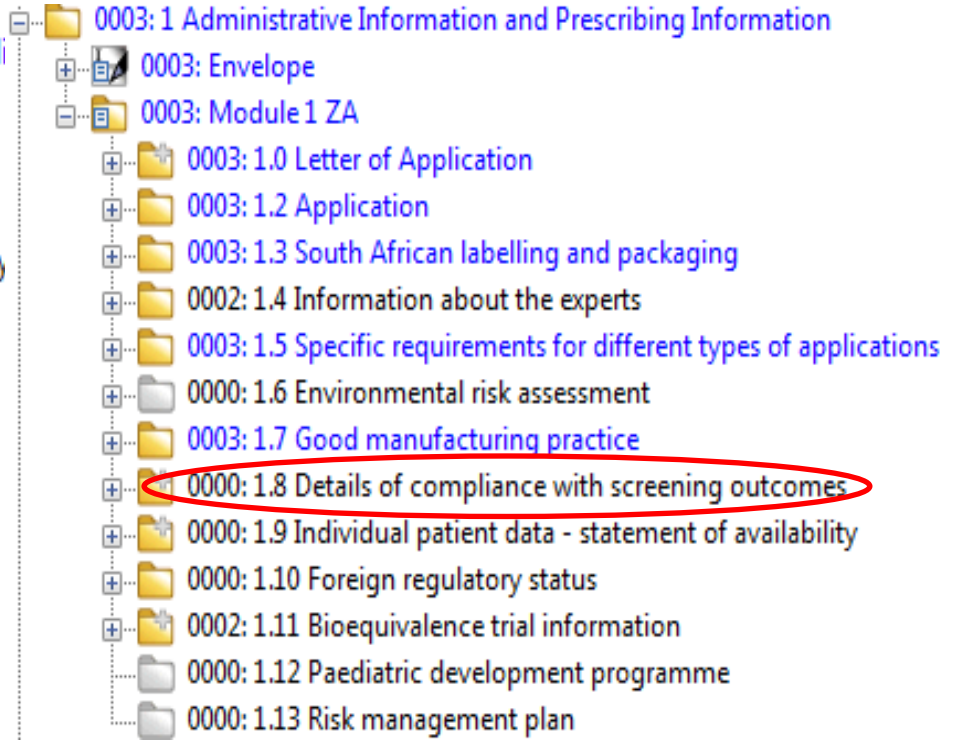
Element 1.3 South African labelling and packaging

- The annotated PI and PIL should be included in M1.5.5
- The annotated documents could at first not be located and were then found in M1.3.1/2 as one document each.
- In view of the life cycle issues created by documents submitted in the incorrect folders, the submission cannot be accepted.

Business validation *cont.*



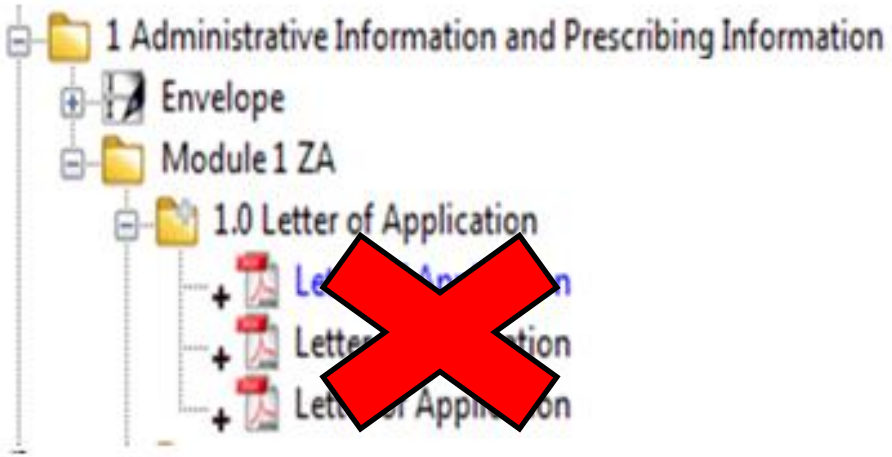


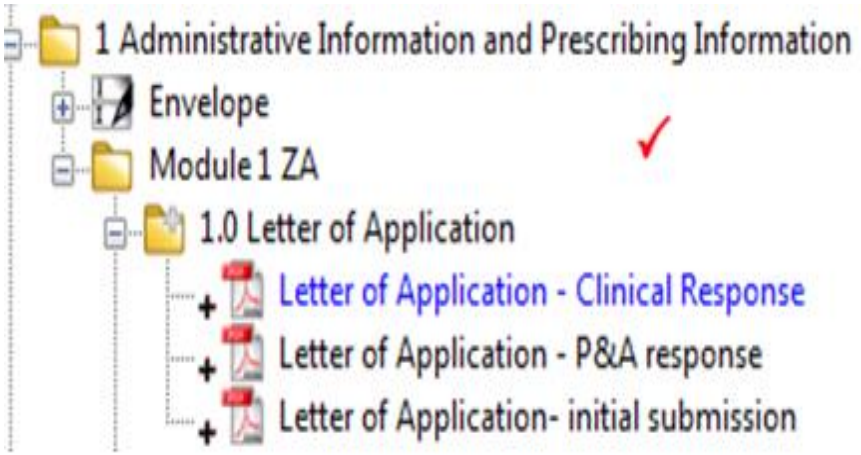


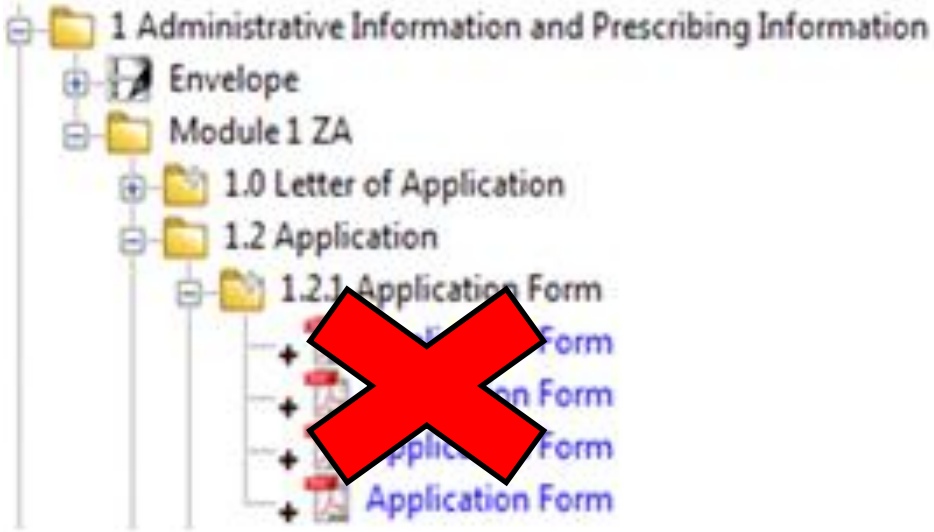
Leaf titles

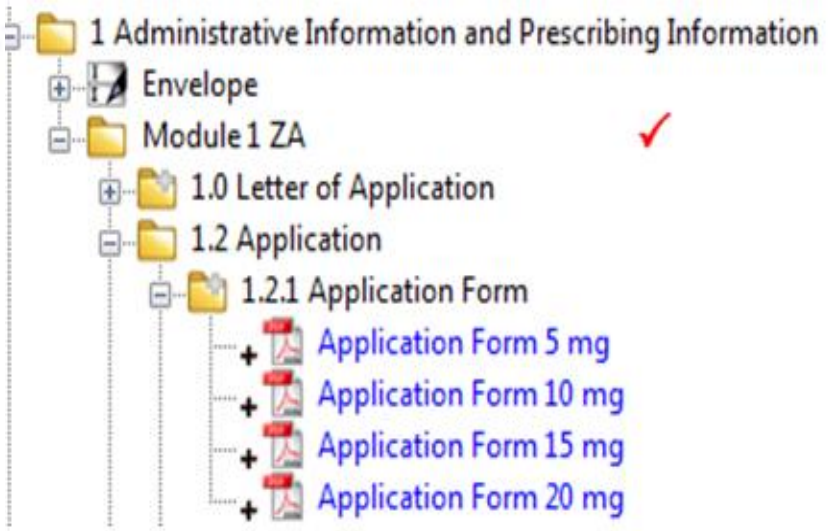
- Each document in the eCTD has both a **file name** and a **leaf title.**
- File name is the actual name of the file – the evaluator doesn't see this
  - e.g. application-letter-10mg.pdf and label-10mg.pdf are the file names
- **Leaf title** is displayed when the evaluator views the submission
- Should be sufficiently descriptive and brief

Leaf titles *cont.*

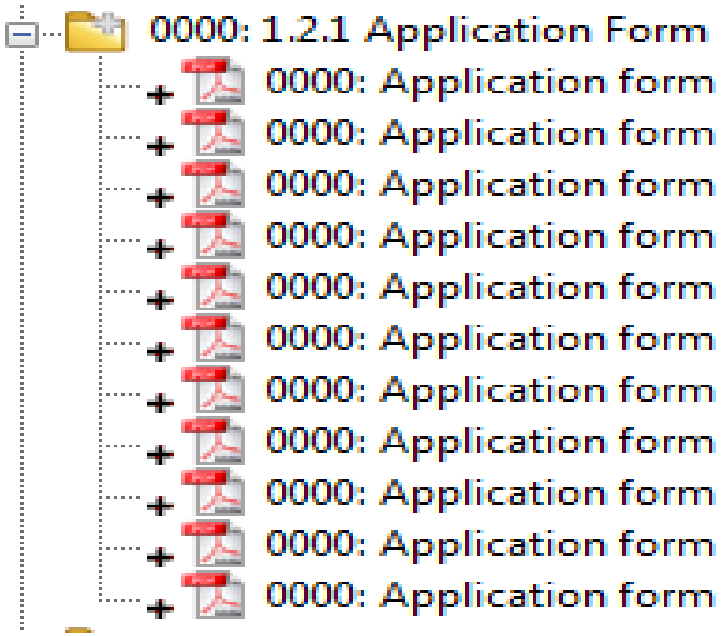


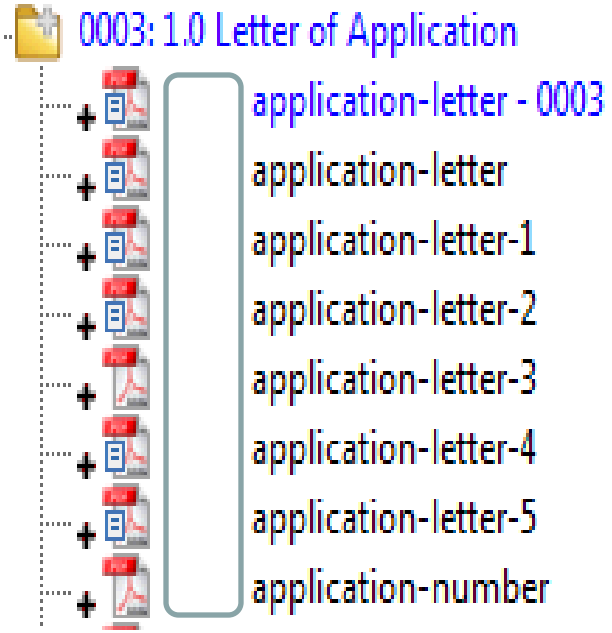


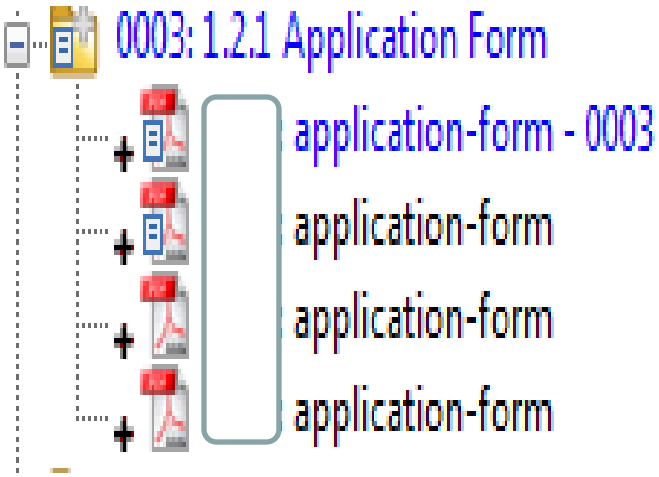




Business Validation *cont.*



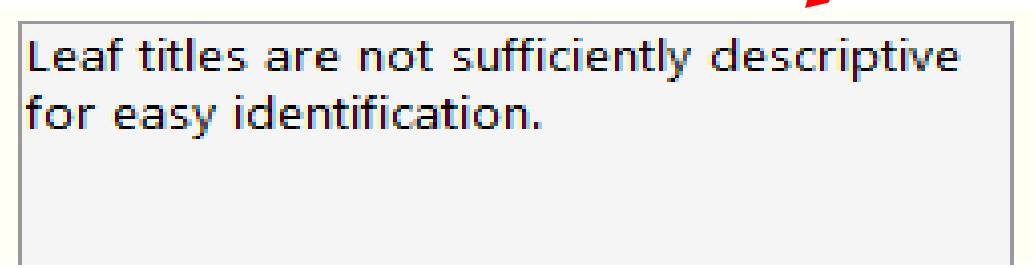




Business validation – *cont.*

Validation template

7	Are leaf titles descriptive and logical, e.g. for applications with various strengths, and new documents in follow up sequences?		Y ☐√ N ☐

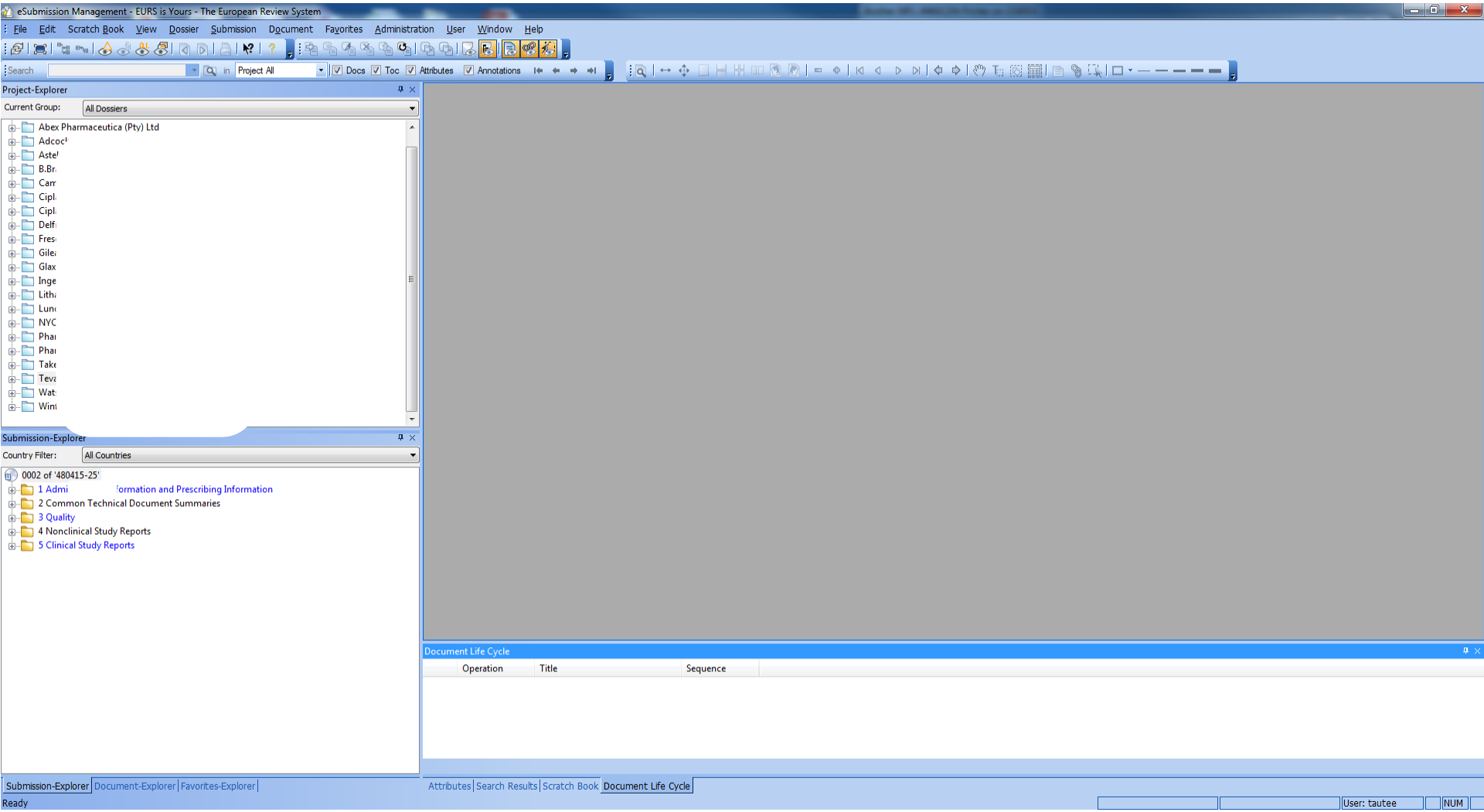


Validation failure

- Technical validation failure:
  - Replacement sequence required
  - “Screening” fee again payable
- Business validation failure:
  - Next sequence will be required
- ……Delay

Evaluation phase

What does evaluator see



What does evaluator see

- 0002: 1 Administrative Information and Prescribing Information
  - 0002: Envelope
  - 0002: Module 1 ZA
    - 0002: 1.0 Letter of Application
      - 0002: Annex 1.1 - P&A Recommendation Letter
      - 0002: Annex 1.2 - Clinical Committee Recommendation
      - 0001: Application Letter Amendment 0001
      - 0002: Letter of application for Sequence 0002
      - 0000: Letter of application
      - 0001: MCC Letter Requiring Amendment 0001
      - 0000: MCC response letter dated: 17/09/2013
      - 0002: Reviewers Guide
      - 0000: Reviewers Guide
      - 0001: Tracking Table 0001
      - 0000: Tracking Table
      - 0002: Tracking Table
    - 0002: 1.2 Application
    - 0002: 1.3 South African labelling and packaging
    - 0000: 1.4 Information about the experts
    - 0002: 1.5 Specific requirements for different types of applications
    - 0000: 1.6 Environmental risk assessment
    - 0002: 1.7 Good manufacturing practice
    - 0002: 1.8 Details of compliance with screening outcomes
    - 0000: 1.9 Individual patient data - statement of availability
    - 0002: 1.10 Foreign regulatory status
    - 0000: 1.11 Bioequivalence trial information
    - 0000: 1.12 Paediatric development programme
    - 0000: 1.13 Risk management plan
- 0000: 2 Common Technical Document Summaries
- 0002: 3 Quality
- 0000: 4 Nonclinical Study Reports
- 0002: 5 Clinical Study Reports

- 1 Administrative Information and Prescribing Information (106)
  - Envelope
  - Module 1 ZA (106)
    - 1.0 Letter of Application (12)
      - Annex 1.1 - P&A Recommendation Letter
      - Annex 1.2 - Clinical Committee Recommendation
      - Application Letter Amendment 0001
      - Letter of application for Sequence 0002
      - Letter of application
      - MCC Letter Requiring Amendment 0001
      - MCC response letter dated: 17/09/2013
      - Reviewers Guide
      - Reviewers Guide
      - Tracking Table 0001
      - Tracking Table
      - Tracking Table
    - 1.2 Application (43)
    - 1.3 South African labelling and packaging (11)
    - 1.4 Information about the experts (3)
    - 1.5 Specific requirements for different types of applications (6)
    - 1.6 Environmental risk assessment
    - 1.7 Good manufacturing practice (22)
    - 1.8 Details of compliance with screening outcomes (2)
    - 1.9 Individual patient data - statement of availability (1)
    - 1.10 Foreign regulatory status (5)
    - 1.11 Bioequivalence trial information (1)
    - 1.12 Paediatric development programme
    - 1.13 Risk management plan
- 2 Common Technical Document Summaries (20)
- 3 Quality (101)
- 4 Nonclinical Study Reports (2)
- 5 Clinical Study Reports (57)

Evaluation phase

Content – compliance with requirements

- Searchable
- Navigation

However

- Not possible to copy text as documents are not OCR scanned
- Documents not in correct section
- Module 3.2.R not completed
  - Not applicable to generics only
- Whole module numbered, instead of per document

How to locate documents in eCTD

Hypertext linking and Bookmarks

ICH eCTD Specification v3.2.2

- Appendix 3 & 7

2.23 Submission in eCTD format

Leaf titles

2.23 Submission in eCTD format

Bookmarks

Documents exceeding 5 pages that contain multiple headings/sections, tables, figures

- Provide enough bookmarks for easy navigation in the document
- Use meaningful names
- ToCs that are hyperlinked
- List of tables/figures if included

Hyperlinks

Include at least the following hyperlinks:

- Cross-references in the package insert (1.3.1.1) to the actual references
- Cross-references in the Patient Information Leaflet (1.3.2) to the package insert (1.3.1.1)
- References in Sections B to D of the Screening template (1.8) to the documents in the eCTD
- Summaries in Module 2 to the relevant documents in Modules 3 to 5
- Document Table of Contents (ToC) to the corresponding section in the document

Hyperlinks *cont.*

Check the hyperlinks before submitting:

- Are there any broken hyperlinks?
- Do all hyperlinks go to correct destinations?
- Are all external hyperlinks removed?

  (e.g. web links, e-mail links)
- Do hyperlinks appear as **blue text** or blue box links if blue text isn't possible?
- Are hyperlinks set to Inherit Zoom?

What does reviewer see

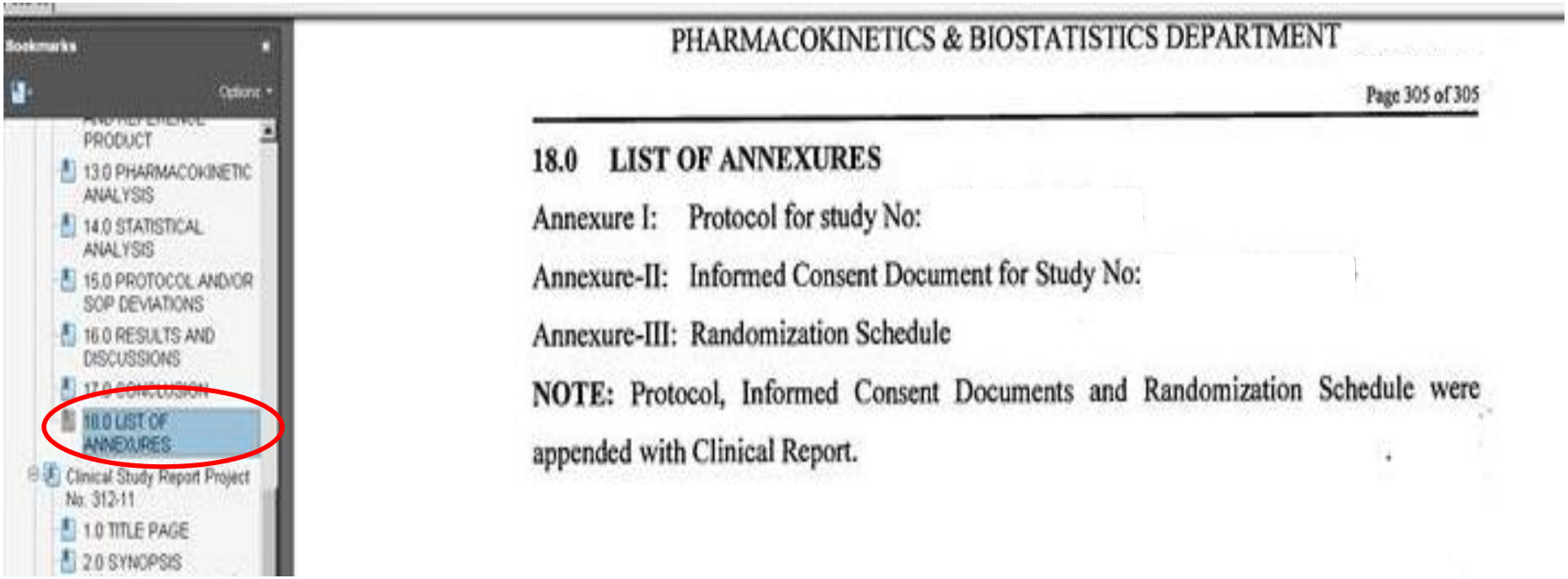
Bookmarks & Hyperlinks

16.0 APPENDICES

Appendix No.	Title
16.1	Study Information
16.1.1	Protocol and protocol amendments
16.1.2	Sample case record forms
16.1.3	List of IECs or IRBs – Representative written information for subject and sample consent forms
16.1.4	List and description of investigators and responsible persons
16.1.5	Signatures of investigators
16.1.6	Listing of subjects receiving test drug(s) / investigational medicinal product(s) from specification batches where more than one batch is used.
16.1.7	Randomisation scheme and codes (Subject identification and treatment assigned)
16.1.8	Audit certificates
16.1.9	Documentation of statistical methods
16.1.10	Documentation of inter-laboratory standardization methods
16.1.11	Publications based on the study
16.1.12	Important publications referenced in the report
16.2	Subject Data Listings
16.2.1	Discontinued subjects

Appendices not hyperlinked.
Documents that follow this list of Appendices are not the Appendices numbered, also not in the same order as the list of Appendices

Bookmarks & Hyperlinks *cont.*



How should the reviewer locate the Annexures?

So evaluation will stop!

Conclusion

Presentation and *content* issues in CTD manifest in eCTD

- Read the guidelines
- Follow the guidelines
- Check the submission
- Think like an evaluator

Electronic is not as patient as paper

- Paper is forgiving – can slot in extra pages or replace documents just before submission
- eCTD is not forgiving – last minute changes will lead to checking of hyperlinks, re-validation, re-export

Conclusions from pilot phase *cont.*

- Concessions made in the pilot phase may no longer be possible when going live
- Importance of quality control apparently not understood
- Evaluation will not continue if there are insufficient bookmarks & hyperlinks
- Incorrect lifecycle attributes or placement of documents will lead to validation failure
- IT support crucial – industry and agency
- Co-ordination of Committees recommendations sent to applicants also for CTD

eCTD roll-out

eCTD roll-out

2.26_CTD_implementation_road_map_Feb16_v6

Start Operational Phase

- *Step 4(a): eCTD process open to entire industry for new applications for registration of NCEs -* ***01 April 2016***
- *Step 4(b): eCTD process open to entire industry for new applications for registration of generics - 02 January 2017*

To date 8 NCEs accepted
5 submitted, 1 failed business validation

eCTD roll-out

Review of Guidelines & technical requirements

- Amendment of validation rules, based on EU, and ZA requirements e.g.
  - Folder structure check
  - Eliminate “append”
  - Compulsory documents and lifecycle attribute

A Letter of application must exist in section 1.0.	9.1	ZA Module 1	P/F	
The operation attribute of the Letter of application must be new.	9.2	ZA Module 1	P/F	
An application form must exist in section 1.2.1.	9.3	ZA Module 1	P/F	One or several application forms can be added to this section. For more information please refer to the Guidance for the Submission of Regulatory Information in eCTD format.
The operation attribute of the Application form should be new.	9.BP1	ZA Module 1	BP	For more information please refer to the Guidance for the Submission of Regulatory Information in eCTD format.

Review of Guidelines & technical requirements

Update of guidance and specification, e.g.

- More information on hyperlinks and bookmarks
- The maximum individual acceptable file size is approximately 200 MB.

  If a file size exceeds 200 MB, the file should be split into two files. The file size should ensure clarity, speed of download and ease of review.
- Include 3.2.R structure

32r-reg-info	
32r1-availability	folder required and additional folders optional
overview-var.pdf	
ref-pdr-var.pdf	
coa-var.pdf	
avail-var.pdf	
32r2-parent-api-diff-sites	folder required and additional folders optional
statement-var.pdf	
32r3-cep	folder required and additional folders optional
cep-var.pdf	
32r4-multiple-api-mnf	folder required and additional folders optional
comp-rep-var.pdf	
comp-results-var.pdf	
compliance-guidelines-var.pdf	
coa-var.pdf	
32r5-med-dev	folder required and additional folders optional
med-dev-var.pdf	
32r6-animal-human-orig	folder required and additional folders optional
origin-var.pdf	
32r7-bmr	folder required and additional folders optional
bmr-var.pdf	
32r8-other	folder required and additional folders optional
other-var.pdf	

Review of Guidelines & technical requirements

- Amendment of Envelope
  - Response to pre-registration recommendation identifies specific Committees' recommendations
  - Submission type: unique ⟹ repeatable
  - *Until such time the type* "**pre-reg-cr:** Response to Council resolutions" *should be used.*

Element¤	Attribute¤	Description/Instructions¤	Constraint¤	Occurrence¤
▪Submission¤	¤	Provides· administrative· information· associated· with· the· submission.¤	Mandatory¤	Repeatable¶ ~~Unique~~¤

eCTD roll-out *cont.*

- Workshop with industry
- Training of additional evaluators

In the mean time

- Working codes
  - As in General Information guideline, preceded by "eCTD" e.g. "eCTD ANA"
- Screening & Application fees
  - Paid with initial sequence, PoP in 1.2.2.1
- Submission media *(4.1 in 2.23 Guidance)*
  - CDs or DVDs – no zip drives, rar-file or any other file format that has been compressed
- Do the quality control

Before you submit, ask...

- If I was an evaluator, could I…….?
  - ✓ Easily locate the information/document
  - ✓ Easily copy and paste from the document
  - ✓ Easily differentiate between same type documents displayed in the eCTD
  - ✓ Easily navigate and access references in documents via bookmarks, links and the Table of Contents
- The ultimate goal is to provide an evaluator-friendly eCTD so that the focus of evaluation is on content, not format.

We all want eCTD……

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