eCTD
Latest updates on the go-live for eCTD in South Africa

SAPRAA

17 November 2017

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Overview

- Products in pilot phase
- eCTD roll-out & Update to guidelines & specifications
- Latest status of the go-live, NCEs & Generics
- Expectations & common deficiencies
  - Presentation, validation & evaluation phases
- Conclusion and hints for industry for successful submissions
- Challenges

Pilot project

Status

- 9 of 18 products registered
  - 5 NCEs
  - 4 Generics and a duplicate
- 1 product rejected by MCC
- 2 products withdrawn by applicants
- 6 products at final stages
- additional strength included for 1 product in the process

eCTD go live

eCTD go live

- Amendment of specifications, validation requirements & guidelines
- Workshop with Industry in October 2016
- Training of additional reviewers
- Appointment of IT personnel
- Transfer of database to new servers
- Upgrade to new version of EURS

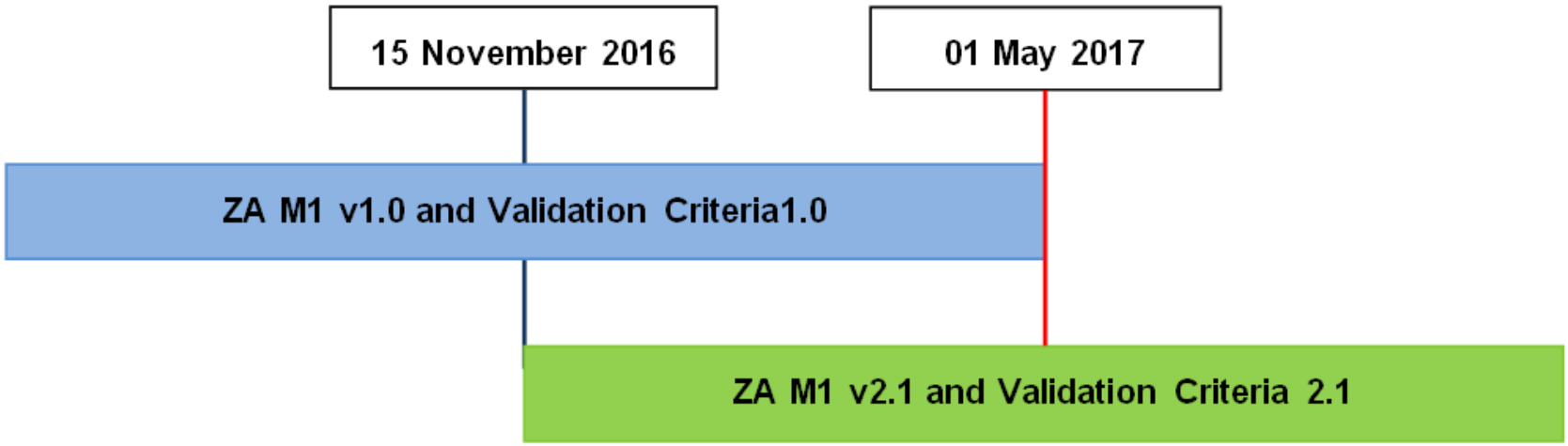
eCTD roll-out

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***

2.29 Implementation Guidance of SA eCTD Module 1 Specification v1.2



New documents

Sept 2016

- Nov 2016 Correction of DTD, editorial changes

- 2.21 South African Specification for eCTD Regional – Module1 - v2.1
- 2.22 Validation criteria for South African Module 1 – v2.1
- 2.23 Guidance for Submission of Regulatory Information in eCTD format – v2.0
- 2.27 eCTD checksums – v2.0
- 2.29 eCTD Implementation Guide – v1.2
- 2.28 eCTD Q&A – v3
- 6.16 Validation template – v2.0

Changes in Guidance

Electronic copy declaration

- The paper version is to be arranged in the same order as the electronic version. An electronic copy declaration should be submitted in Module 1.2.2.4 to confirm that the paper versions are identical to the PDF versions included in the eCTD. As it is a declaration, it must be **signed** and **dated** and indicate the relevant **sequence**.

Changes in Guidance – *cont.*

3.1.1 eCTD Identifier

- The application number is to be used for the top-level directory (root directory). This will be the unique identifier for the application. In the case of **multiple applications** the application number of the **master** application should be used as the eCTD identifier.

3.2 eCTD envelope

- The application number must be included in the envelope. In the case of **multiple applications** the application numbers and proprietary names should be included as follows:
  - application number: master application
  - proprietary name: master application
  - multiple applications: name/s and application number/s of duplicate application/s

Changes in Guidance – *cont.*

3.1.6 Module 3.2.R

- An enhanced granularity is required in this module. The granularity should be built with Node Extensions and Subfolders including **numbering of the subfolders**.

  Further information can be found in the South Africa eCTD Validation Criteria on the tab “File-Folder Structure & Names”.

- **Non-compliance may lead to business validation rejection**

Changes in Guidance – *cont.*

- PDF files
  - The maximum individual acceptable file size is approximately ~~100~~ **200** MB. If a file size exceeds 200 MB, the file should be split into two files
- MD5 checksum
  - 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, and indicate the **product name, application number and relevant sequence.**
- New 4.10 Handling of **thumbs.db** files
- More information on **hyperlinks** and **bookmarks**

Changes in Guidance – *cont.*

Life cycle management of specific documents

The operation attribute should always be "**New**" for the following leaf elements provided with all eCTD-sequences:

- **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 amendments**

Checked in validation

For the application form leaf elements the operation attribute may be "replace" only if it had to be corrected.

Tracking table submitted as a separate document has no lifecycle - operation attribute "new".

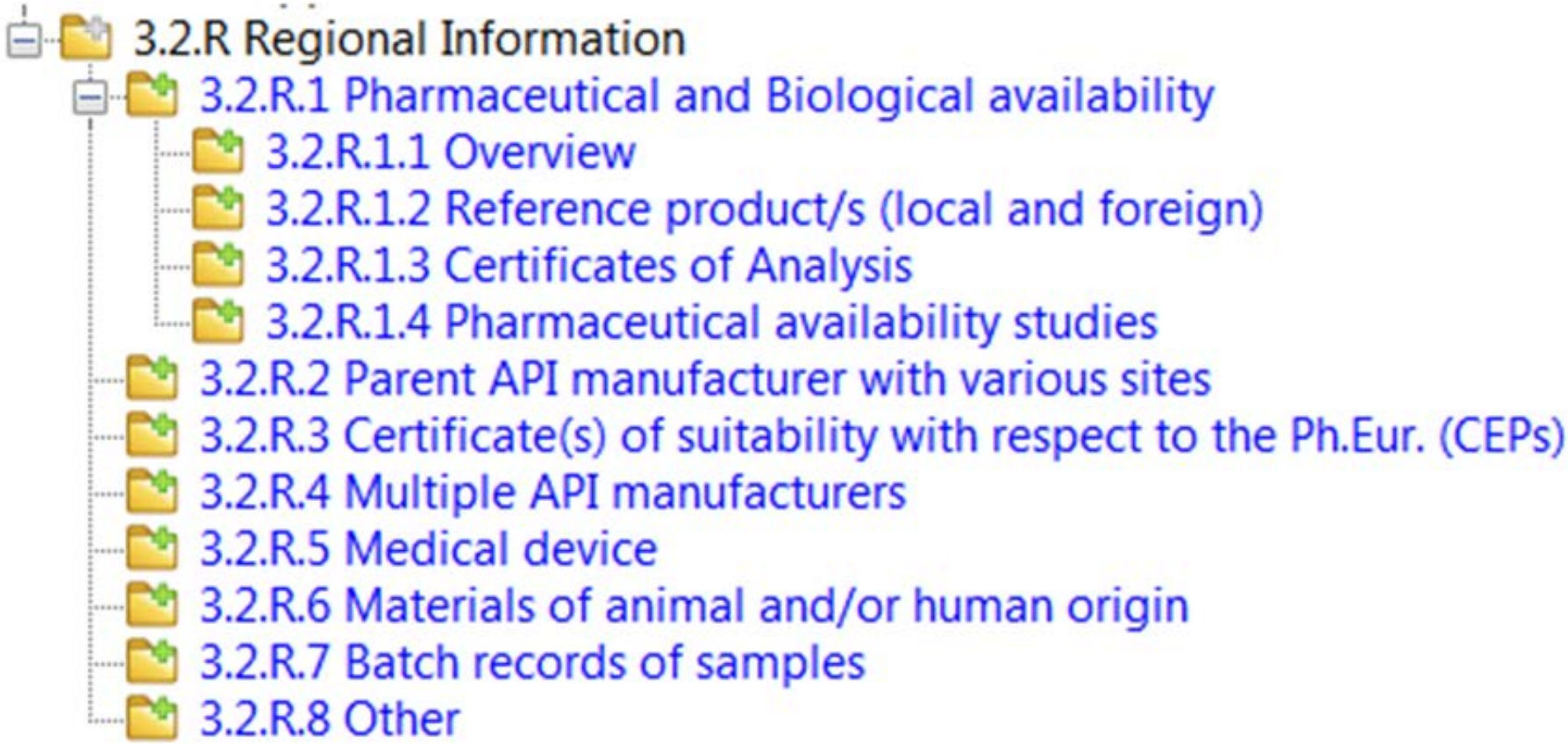
Structure of 3.2.R

File and folder names controlled by new validation criteria

32r-reg-info	
32r1-availability	folder required
32r11-overview	folder required
overview-var.pdf	
32r12-ref	folder required
ref-prd-var.pdf	
32r13-coa	folder required
coa-var.pdf	
32r14-availability	folder required
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	

Structure of 3.2.R – *cont.*

Specific file and folder structure mandatory for section 3.2.R



Validation template

2	Product application number and eCTD sequence number				

2	Check envelope for correctness of information:				
	• Multiple / duplicate applications – name and application number/s	C	Y ☐	N ☐	N/A ☐

3	PI and PIL				
3.1	Is the PI hyperlinked to the references?	C	Y ☐	N ☐	N/A ☐
3.2	If sequence 0000, has the PI been included in Module 1.3.1.1?	C	Y ☐	N ☐	N/A ☐
3.3	If sequence 0000, has the PIL been included in Module 1.3.2?		Y ☐	N ☐	N/A ☐
3.4	Is the PIL hyperlinked to the PI?	C	Y ☐	N ☐	N/A ☐
3.5	For amendments / responses, have the annotated PI and PIL been included in Module 1.5.5?		Y ☐	N ☐	N/A ☐

5	Is the Tabulated Schedule of Amendments hyperlinked to the new / updated data (pharmaceutical) ?	C	Y ☐	N ☐	N/A ☐
6	Module 3.2.R				
	• Is it structured according to correct granularity	C	Y ☐	N ☐	N/A ☐
	• Are the node extensions numbered according to the relevant section		Y ☐	N ☐	N/A ☐

Validation template – *cont.*

7	For follow up sequences, is the operation attribute of the following documents reflected as "new"		
	• 1.0 Letter of application	C	Y ☐ N ☐
	• 1.2.1 Application form	C	Y ☐ N ☐
	• 1.2.2.1 Proof of payment		Y ☐ N ☐ N/A ☐
	• 1.2.2.4 Electronic copy declaration	C	Y ☐ N ☐
	• 1.5.2.1 Tabulated schedule of amendments	C	Y ☐ N ☐

Now controlled with Validation criteria!

Validation criteria

- Rules revised in line with the EU and ZA requirements
- Clarification of rules 9BP1, 2, 3 re ***operation attribute***
  - Not for submission types Withdrawal and Cancellation
- Clarification of rules 9BP8, 9 re ***amendment schedule***
  - Reference to guidance included and “some” for submission types
- Correction of filename in section 3.2.R.1.2

New validation criteria

- Documents to be present & Lifecycle e.g.

9.1	ZA Module 1	A Letter of Application must exist in section 1.0.	P/F
9.2	ZA Module 1	The operation attribute of the Letter of Application must be new	P/F

Also:

- 9.3 An **Application Form** must exist in section 1.2.1
- 9.4 An **electronic copy declaration** must exist in section 1.2.2.4
- 9.5 A **Validation Template** has to exist in section 1.8
- 9.BP9 A **Tabulated Schedule of Amendments** should exist in section 1.5.2.1

New validation criteria – *cont.*

Lifecycle

- 9.BP1, 2, 3, 4

  The operation attribute to be **new**

  - Application Form
  - Proof of Payment
  - Electronic copy declaration
  - Tabulated Schedule of Amendments

New validation criteria – *cont.*

- Hyperlinks e.g.

9.BP5	ZA Module 1	The cross-references in the Patient Information Leaflet in section 1.3.2 should be hyperlinked to the package insert in section 1.3.1.1.	BP
9.BP6	ZA Module 1	The cross-references in the package insert in section 1.3.1.1 should be hyperlinked to the actual references.	BP
9.BP7	ZA Module 1	The references in Sections B to D of the Validation template in section 1.8 should be hyperlinked to the respective documents in the eCTD.	BP
9.BP8	ZA Module 1	The references in the "Tabulated Schedule of Amendments" should be hyperlinked to the relevant documents dealing with the recommendations and responses.	BP

New validation criteria – *cont.*

- 3.2.R structure

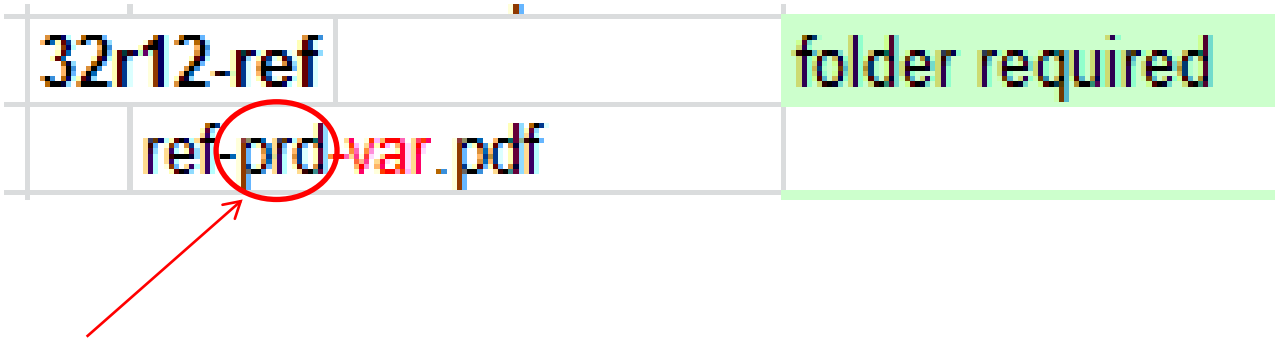
14.BP5	Files/folders	If documents are placed in section 3.2.R (including subfolders), the structure must follow the structure given in the ZA M1 specification.	BP

- Related sequence

21.BP1	Envelope Attributes	If the submission type is a Response to a pre-registration recommendation or post-registration, then the related sequence attribute is a four digit number.	BP
21.BP2	Envelope Attributes	If the submission type is not a Response to a pre-registration recommendation or post-registration, then the related sequence attribute must be "none".	BP

New validation criteria – *cont.*

- Additional rules re PDF settings under 20.PDF files
- Cross-sectional lifecycle under 19. Modified File
- Correction in file folder structure & names for 32R



SA Specification – Regional – M1

Sept 2016	Amendment of sections Abbreviations & Acronyms, Definitions, 2, 3.1, 4, Appendix 1, Appendix 2 (Table 5), Appendix 3, Appendix 4 Added section 7.6	v2 October 2016
Sept 2016	Correction of DTD, editorial changes	v2.1 November 2016
01 May 2017	Implementation	

- **New**: 7.6 Folder and Filename path length
- Appendix 2: Envelope Element Description

Changes in the envelope

- **Submission type** – occurrence changed from “unique” to “**repeatable**”
  - More than 1 submission type can be added to the envelope
- **Changes submission types**
  - **na-cams**: Complementary ~~and Alternative~~ Medicines
  - **pre-reg-cams:** Complementary ~~and Alternative~~ Medicines
  - **post-reg-pa**: Pharmaceutical and ~~&~~ Analytical
  - **post-reg-cams**: Complementary ~~and Alternative~~ Medicines
- **Deleted submission types**
  - ~~**pre-reg-pa-insp:** Pharmaceutical & Analytical and Inspectorate~~
  - ~~**post-reg-pa-insp**: Pharmaceutical & Analytical and Inspectorate~~

Changes in the envelope – *cont.*

- **New submission types**
  - Response to post-registration recommendation
  - Baseline submissions

- **multiple / duplicate applications**
  - Replaced "**date** of applications" with "application **numbers**"

New submission types

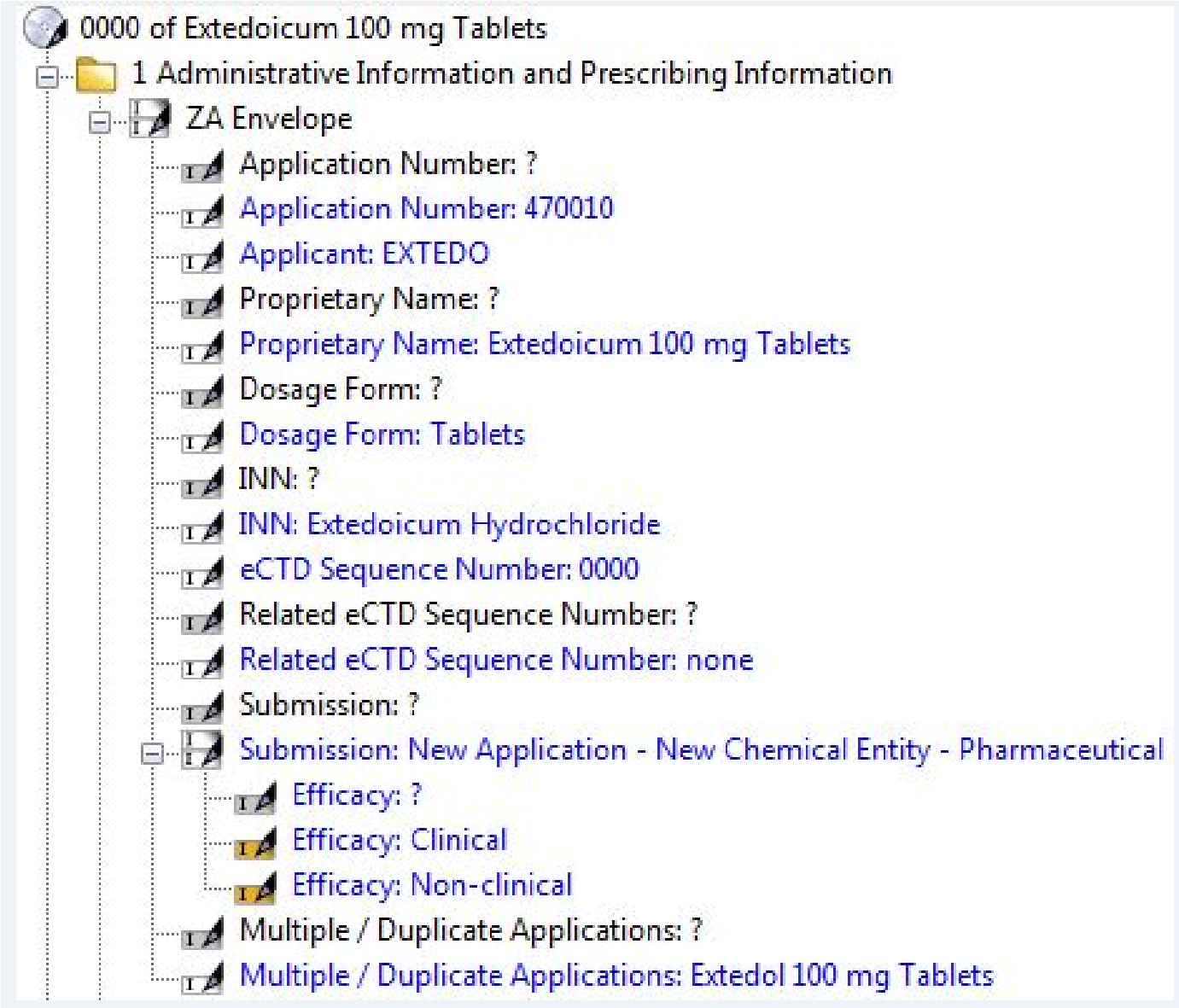
Response to post-registration recommendation:

- **resp-post-reg-insp:** Inspectorate
- **resp-post-reg-pa:** Pharmaceutical and Analytical
- **resp-post-reg-cl:** Clinical
- **resp-post-reg-pn:** Proprietary name change application
- **resp-post-reg-pn-update:** Updates following a proprietary name change approval
- **resp-post-reg-hcr:** Applicant transfer, name and address change of applicant
- **resp-post-reg-biol:** Biologicals and biosimilars
- **resp-post-reg-cm:** Complementary Medicines

Baseline submissions:

- **baseline**: Reformatting from Paper to eCTD

Structure of envelope



Related sequence

Sequence	Submission Type	Submission Description	Related eCTD Sequence	Submission Type Related Sequence	Comment
0005	pre-reg-cl	Response to second Clinical recommendation for the NCE	0000 0001 0003 0004	na-nce-ph pre-reg-pn pre-reg-cl pre-reg-pa	This is a continuation of the regulatory activity initiated in 0000 and 0003 and includes the approved amended proprietary name, and includes P&A labelling recommendations, so the related eCTD sequence points to the beginning of that activity, the first Clinical response, second P&A response, as well as the Proprietary Name response
0006	post-reg-pa	Application for shelf-life extension of the NCE	<none>	<none>	This is a new regulatory activity and so no related eCTD sequence is included
0007	post-reg-cl	Application for a new indication for the NCE	<none>	<none>	This is a new regulatory activity and so no related eCTD sequence is included
0008	post-reg-pa	Application for an additional API manufacturer for the NCE	<none>	<none>	This is a new regulatory activity and so no related eCTD sequence is included
0009	resp-post-reg-pa	Response to P&A recommendation on the shelf-life extension for the NCE	0006	post-reg-pa	This is a continuation of the regulatory activity initiated in 0006 and so the related eCTD sequence points to the beginning of that activity
0010	resp-post-reg-pa	Response to P&A recommendation on the additional API manufacturer for the NCE	0008	post-reg-pa	This is a continuation of the regulatory activity initiated in 0008and so the related eCTD sequence points to the beginning of that activity
0011	resp-post-reg-cl	Response to Clinical recommendation on the new indication for the NCE	0007	post-reg-cl	This is a continuation of the regulatory activity initiated in 0007 and so the related eCTD sequence points to the beginning of that activity

Go-live NCEs April 2016

- 42 applications
  - 2 (5) withdrawn
- 40 applications – 80 products
  - Includes different strengths and 12 duplicates
- 20 applicants
- 29 submitted
- 1 split on 2 DVDs
- 1 submitted 2 sequences
- 7 failed technical validation
- 26 submissions passed technical & business validation, some with 0001
- 3 resubmissions awaited

Go-live NCEs - *cont.*

Technical	Business
Fail	
Valid	Issues

Valid	Issues

Valid	Issues

Valid	Fail
Valid	Fail
Valid	Issues

Valid	Issues

Valid	Issues

Valid	Issues
Valid	Issues

Valid	Fail
Valid	Issues

Fail	
Valid	Fail

Valid	Fail
Valid	Minor issues

Valid	Fail

Fail	
Valid	Fail

Valid	Fail

Valid	Issues

Fail	
Valid	Fail

Valid	Fail

Valid	Valid

Valid	Fail

Valid	Issues

Valid ! 61 warnings	Issues

Valid	Issues

Valid	Issues

2 sequences - to resubmit as 0000

Unable to validate and import - freezes from ISO & DVD

Go-live Generics January 2017

- 69 applications
- 4 (10) withdrawn
- 65 applications – 191 products
  - Includes different strengths and 63 duplicates
- 19 applicants
- 24 submitted
  - Three failed at administrative screening
  - 1 failed admin & technical validation
  - 3 passed without issues
- 1 CD empty – application withdrawn
- 17 resubmissions awaited

Go-live Generics - *cont.*

Technical	Business
Valid	Valid
Valid	Valid
Valid Many BP warnings	Fail
Valid	Fail
Valid Many BP warnings	Fail
Valid Many BP warnings	Fail
Valid	Fail
Valid	Fail

Requirement vs Actual

Administrative errors

- 2 eCTDs submitted for master + duplicate
- Validation template left blank
- Validation template – *hard copy not included*
- MD5 checksum not identifiable
- Electronic copy declaration illogical
- Electronic copy declaration not signed
- Paper documents not tabbed
- Hard copy of application form not signed
- Latest version of validation template not used
- Sequence number not indicated in template

Administrative errors - *cont.*

- Footers of application form and validation template changed
  - Contrary to confirmation given in validation template
- Amendment schedule attached in hard copy – *not required*
- Virus check statement incomplete
  - Name of virus checker not stated & not confirmed that submission is virus-free
  - Contrary to confirmation in validation template.
- The date of receipt is for this office to complete.

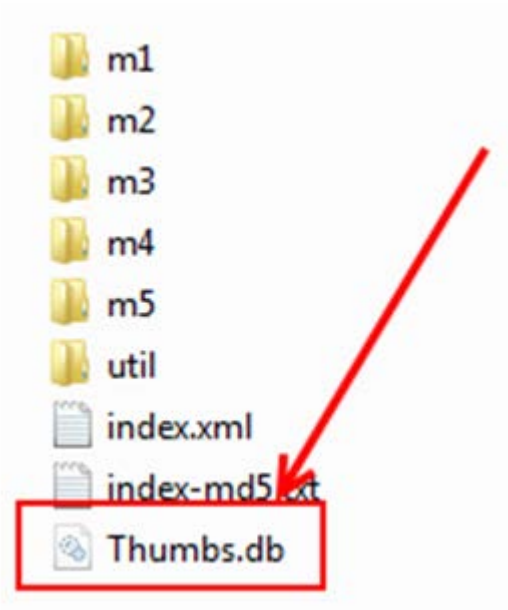
9	Date of letter of application		22 July 2016
10	Date of receipt		22 July 2016

Technical Validation failure

- File or folder name contains invalid characters
  rule 11 → 14.6, 14.7
- DTD checksums not valid
  rules 3-6 → 1.1 – 1.6, 2.3, 3.5, 7.1-7.5, 8.5, 10.3, 11.3, 12.3
- PDF password protected *(rule 18 → 20.2)*
- Unreferenced files *(rule 7 → 14.9)*
- Files in Module 3 missing (export path too long)
- Files corrupted

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.

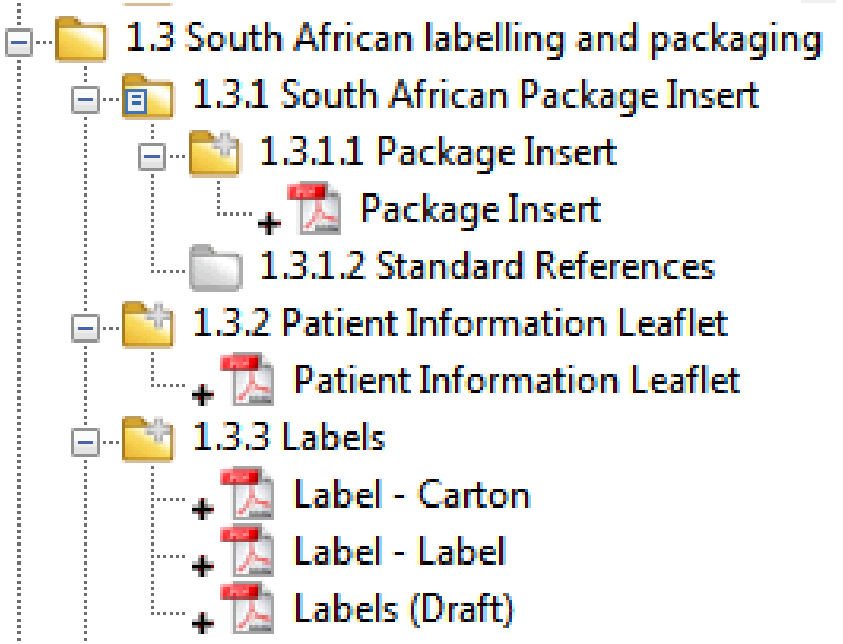
It is possible to disable thumbs.db files in Microsoft Windows.

Business validation

Leaf titles

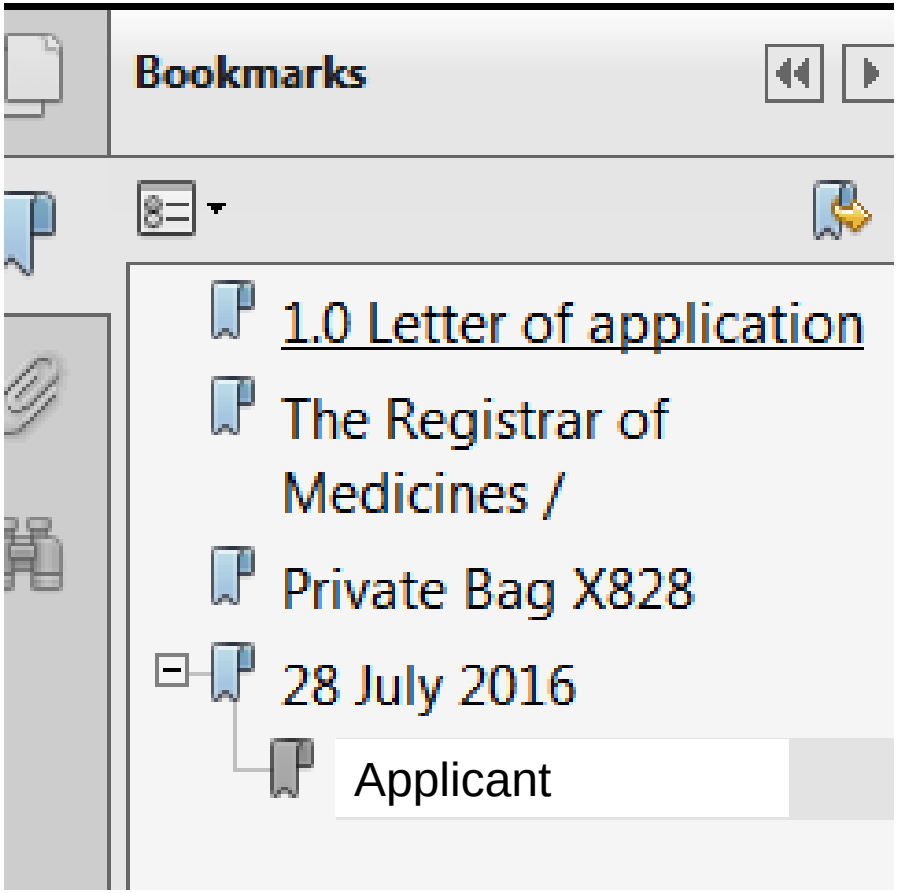
PDF	0000	vap-06relsub
PDF	0000	vap-02water
PDF	0000	vap-04disso
PDF	0000	vap-07iduv
PDF	0000	vap-01all
PDF	0000	Specification(s)

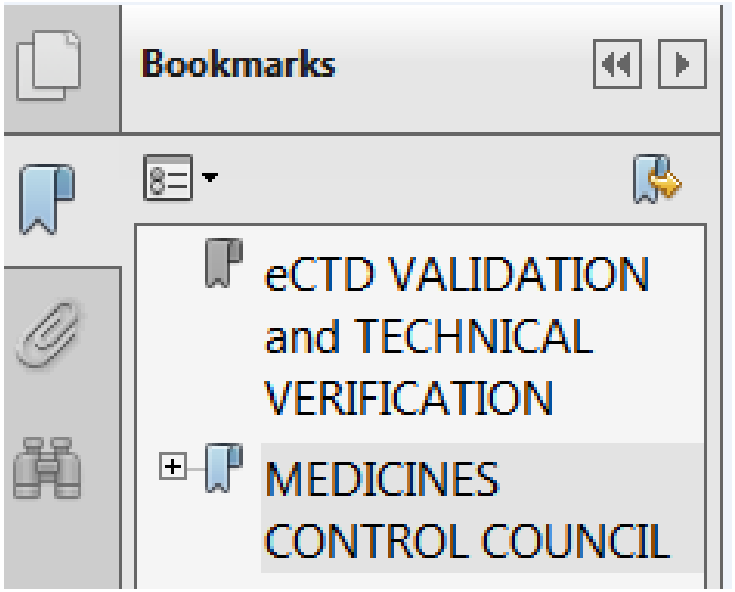
Type	Sequence	Title
PDF	0000	Introduction
PDF	0000	Introduction
PDF	0000	Drug Substance
PDF	0000	Drug Product
PDF	0000	Appendices
PDF	0000	Regional Information
PDF	0000	Nonclinical Overview
PDF	0000	Clinical Overview



Business validation – *cont.*

Bookmarks





Add no value
Formatting of Word document

Business validation – *cont.*

- Envelope data indicated in support of efficacy not the same as in 1.2.1
- 0000 / 0004 / 0006 - Leaf titles are not sufficiently descriptive
- Dates of documents in hard copy and eCTD not the same
- Submission type and related sequences incorrect.
- No amendment schedule submitted
- Copy of the Committees' recommendations not included as an attachment to the letter in M1.0

Business Validation - *cont.*

1.0 Letter of application

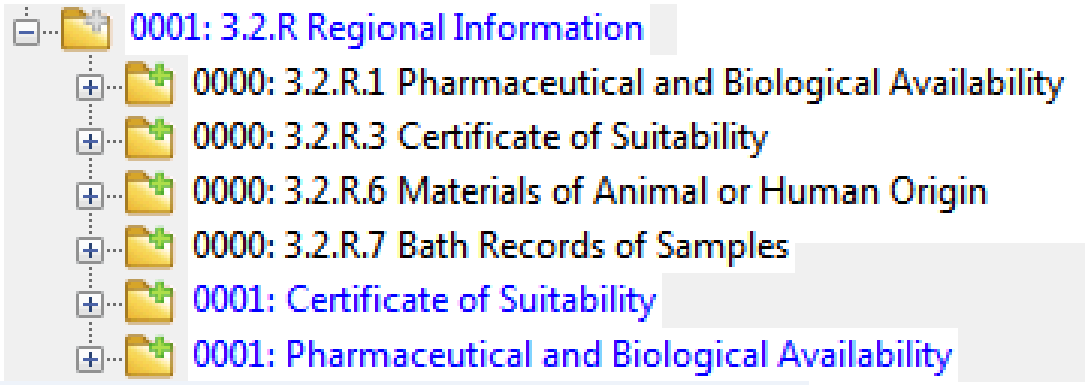
- Amendment schedule should not be an attachment to the letter, but be included in **M1.5.2.1**
- Use of the amendment schedule is not correct:
  - The column for the RMS comment is required.
  - The differences between the current and amended modules have to be indicated.
  - The inclusion of responses to clinical questions as attachments to 1.5.2.1 Tabulated schedule of amendments is not appropriate.

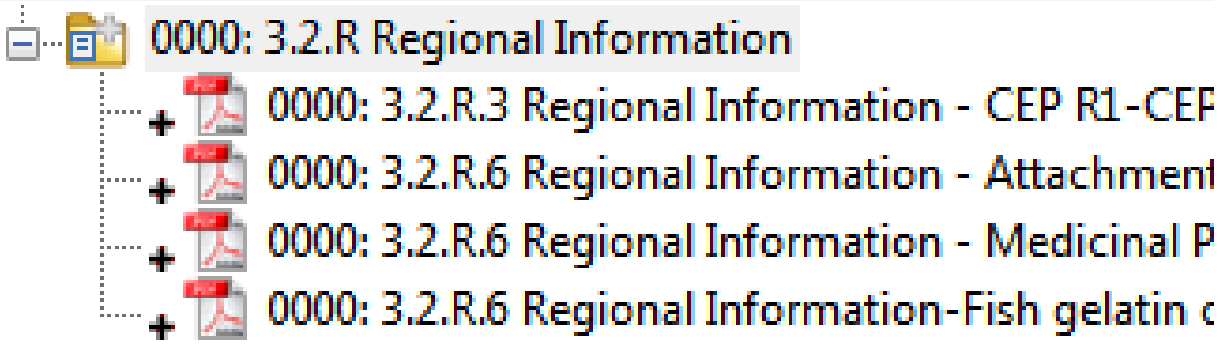
As for a paper submission……

Business validation – *cont.*

3.2.R Regional Information

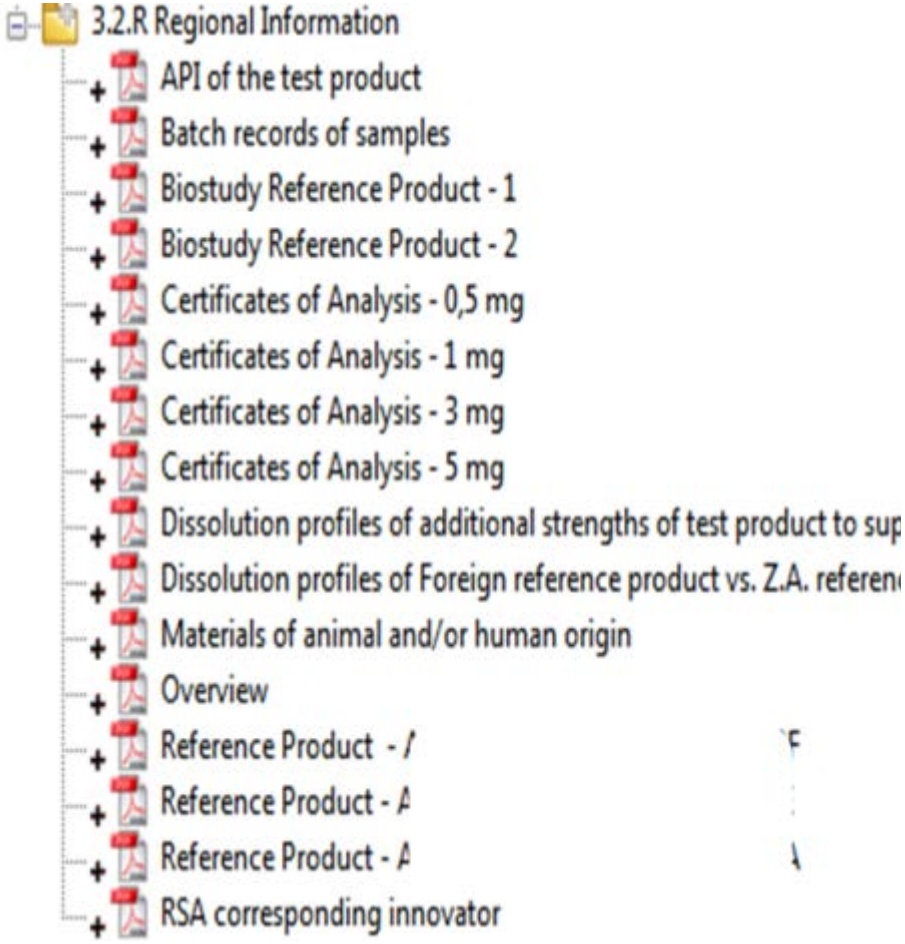
- Node extensions not numbered according to the relevant section, *contrary to the confirmation indicated in the validation template*
- not structured correctly; node extensions not used, naming incorrect.

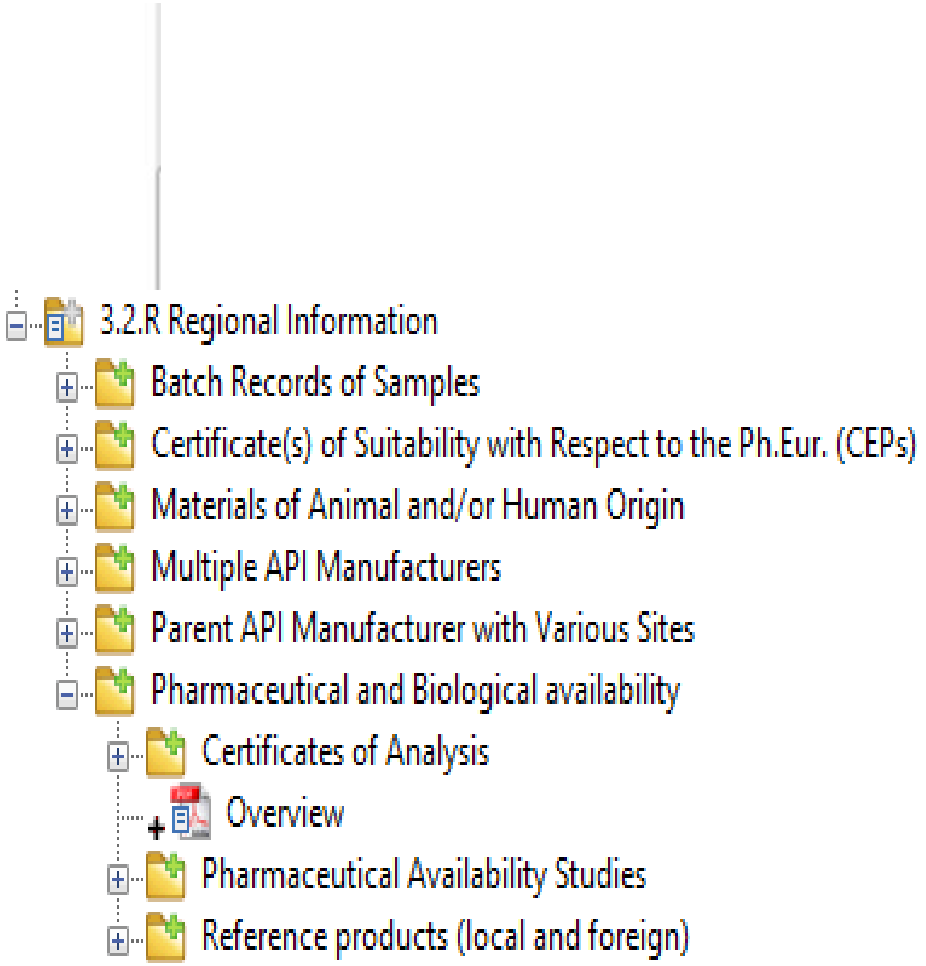




Business validation – *cont.*

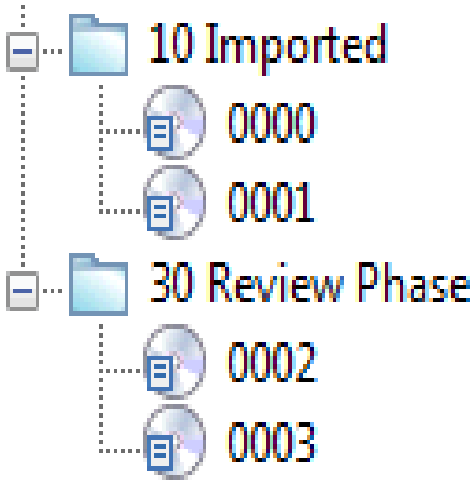
- **3.2.R Regional Information**





Validation failure

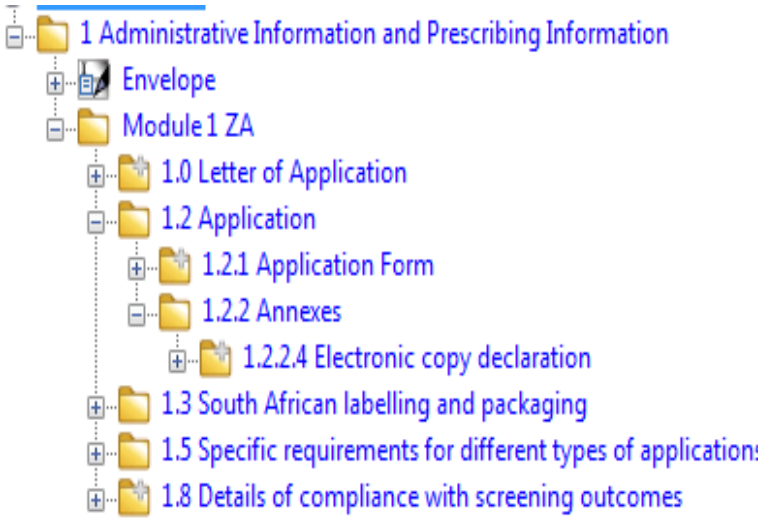
- Technical validation failure:
  - Replacement sequence required
- Business validation failure:
  - Next sequence will generally be required
  - Could require replacement sequence
- Screening (validation) fees again payable
- ……***Delay***



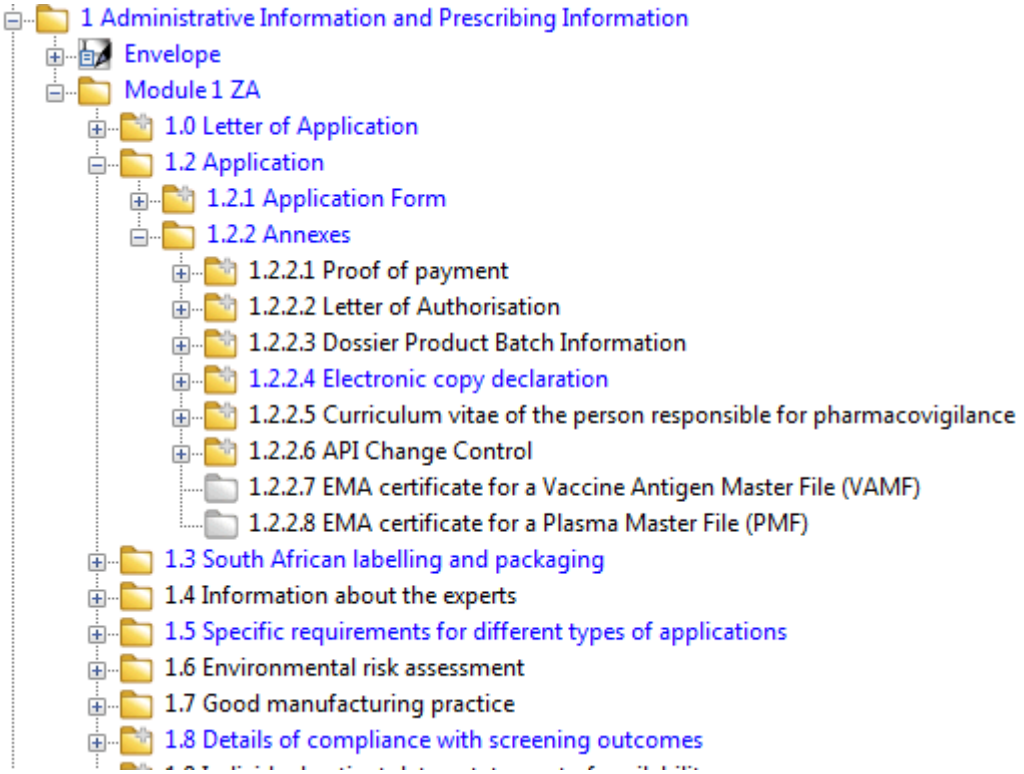
Evaluation phase

What does evaluator see

Delta view

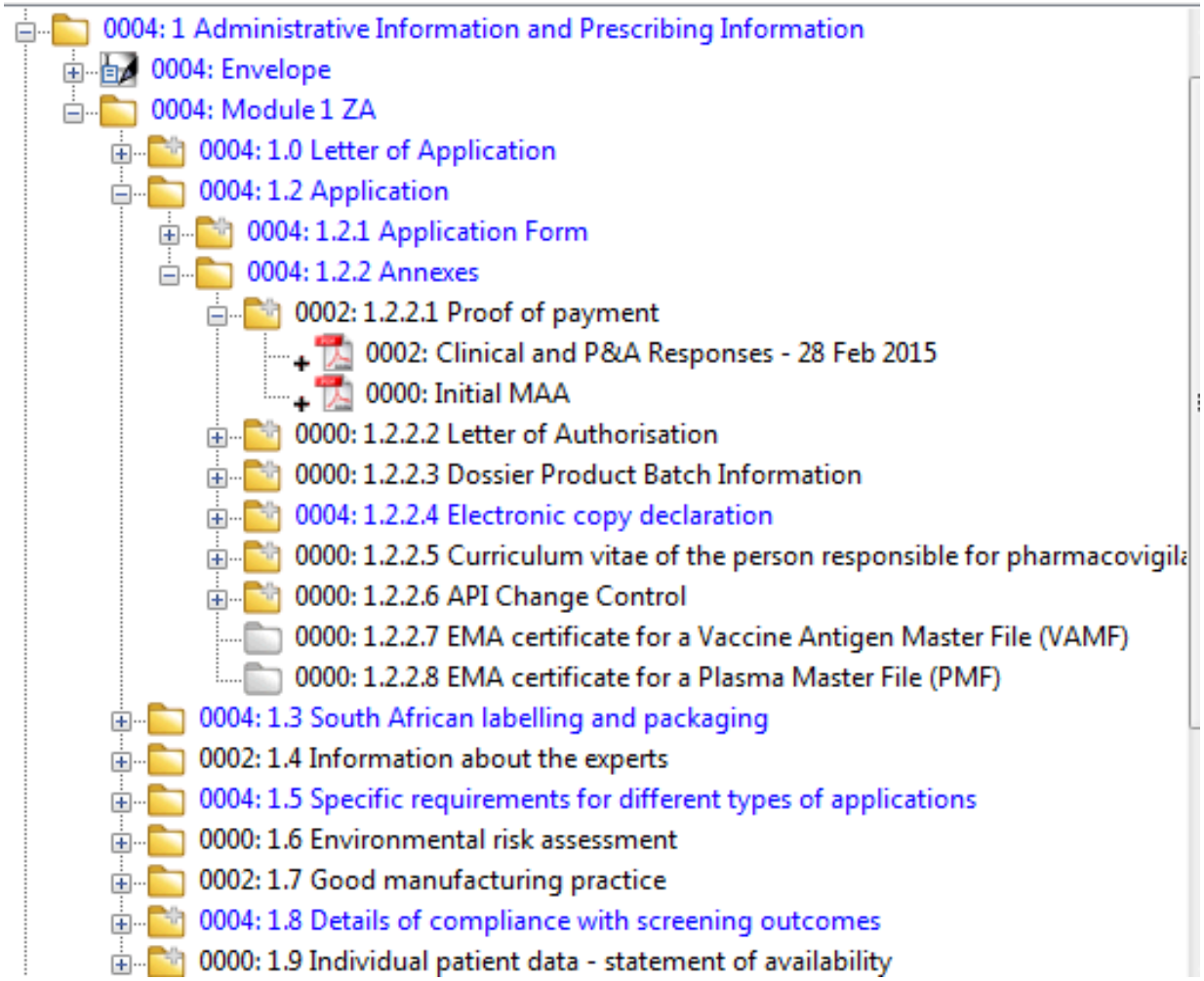


Without Delta view

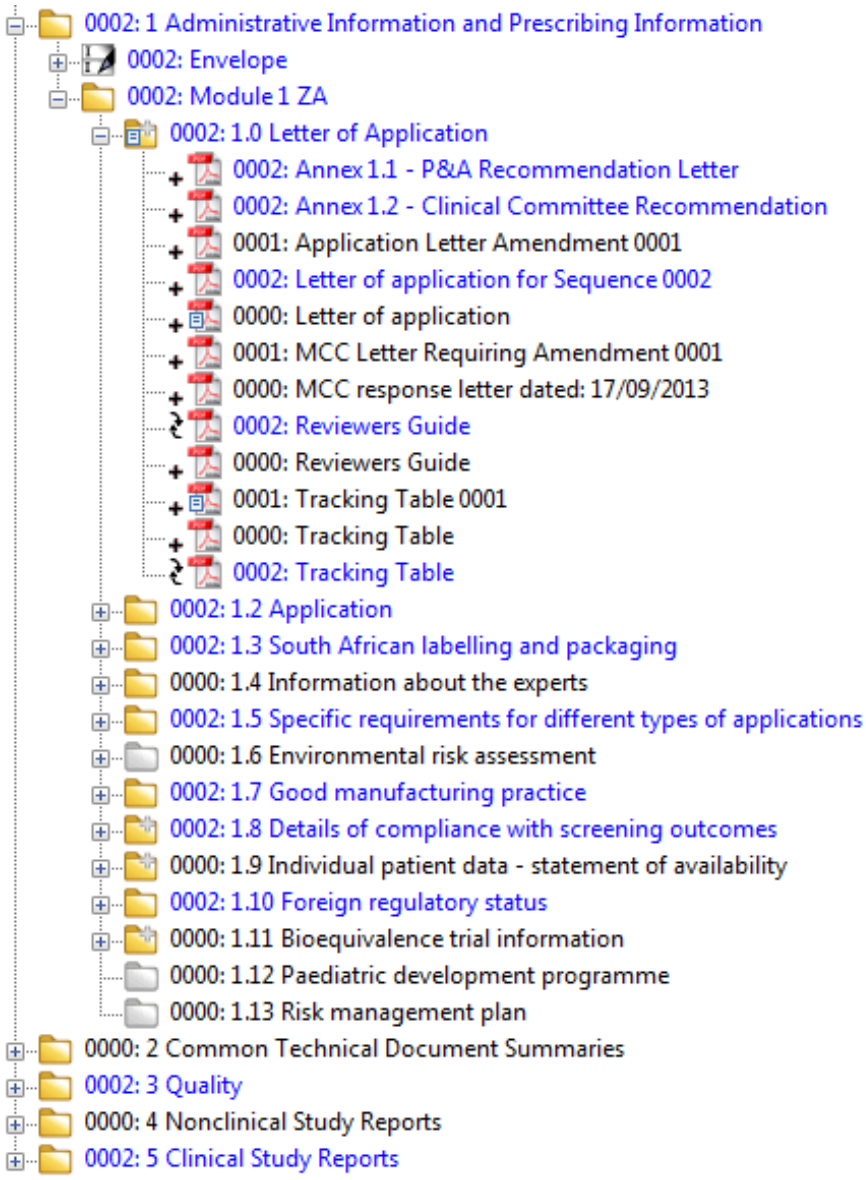


What does evaluator see - *cont.*

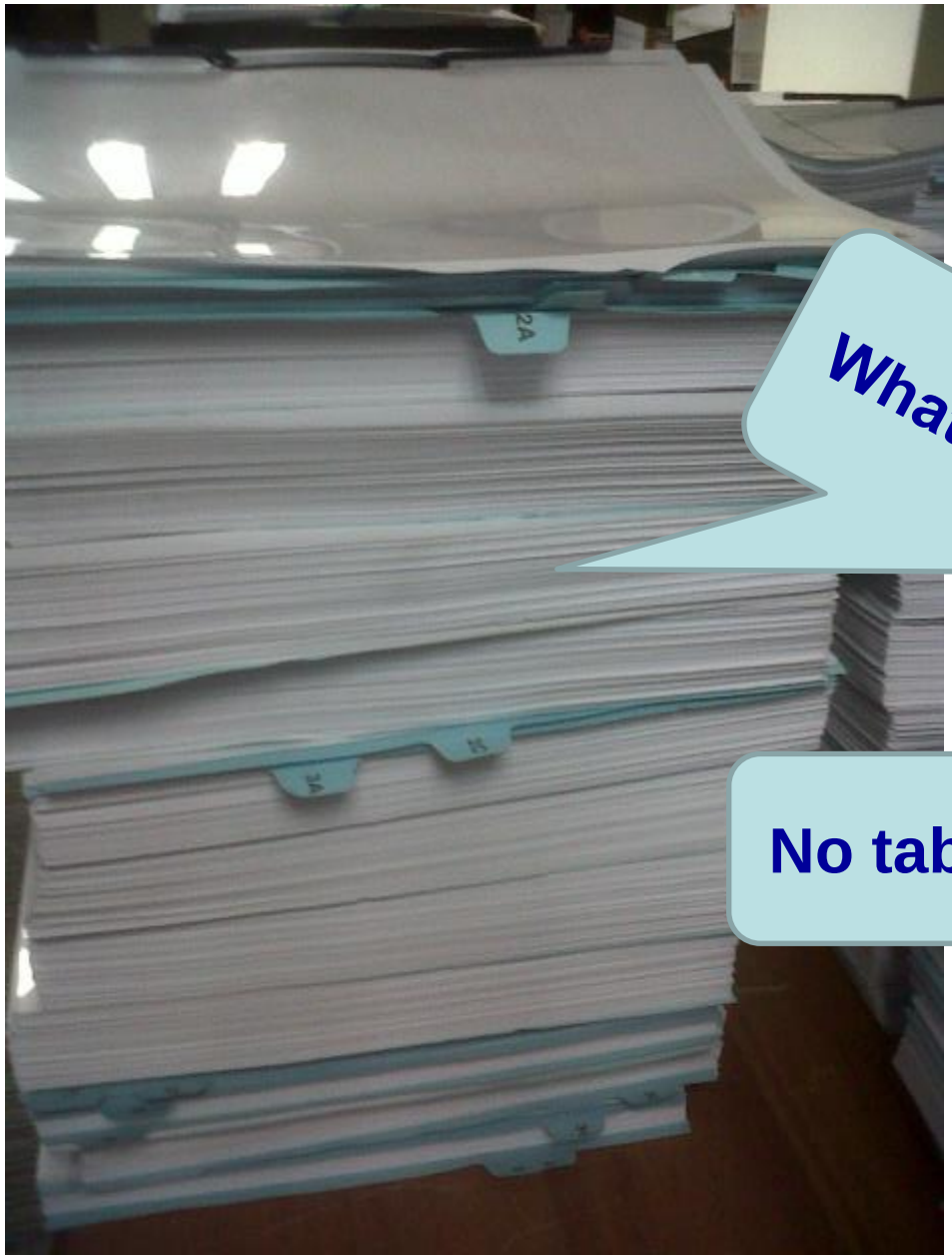
Sequence view



What does evaluator see – *cont.*



How to locate documents in CTD……



What is missing??

No tabbed dividers

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

≡ CTD tabbed dividers

Evaluation phase – *cont.*

- Detail included in the covering letter but not in Amendment Schedule;

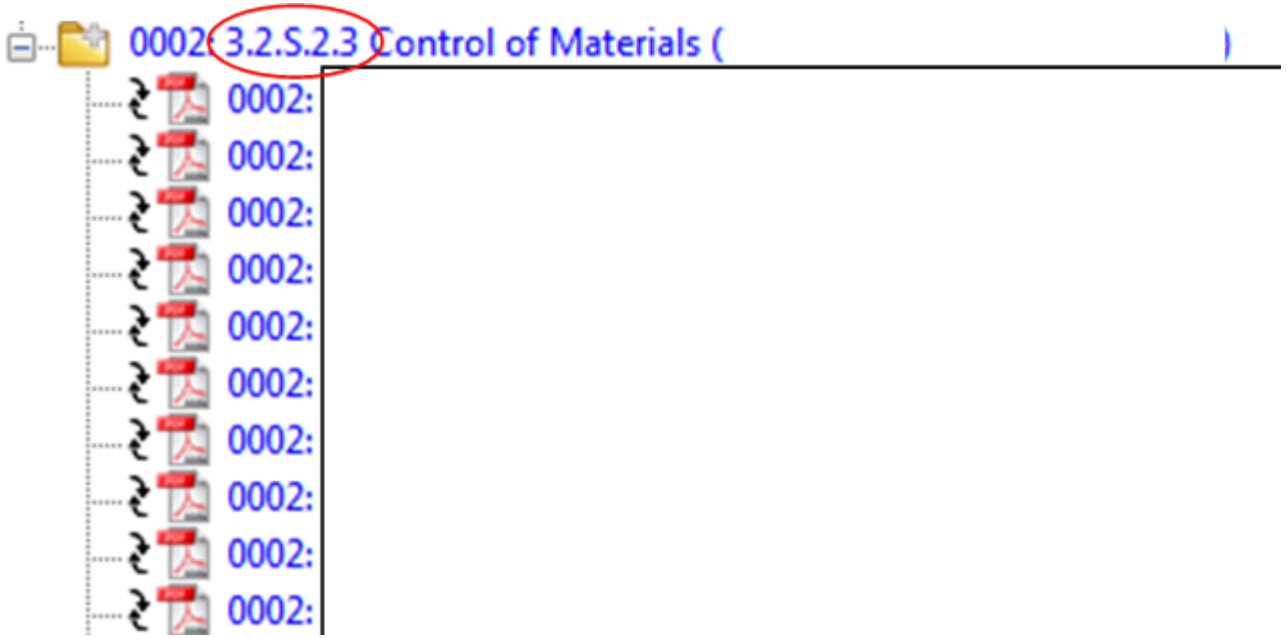
  therefore not possible to verify all information.
- Hyperlinks do not lead to the referenced documents
- Difficult to find relevant information in 32R as node extensions not used
- For an NCE the package insert was hyperlinked to the SPC and not M2/4/5

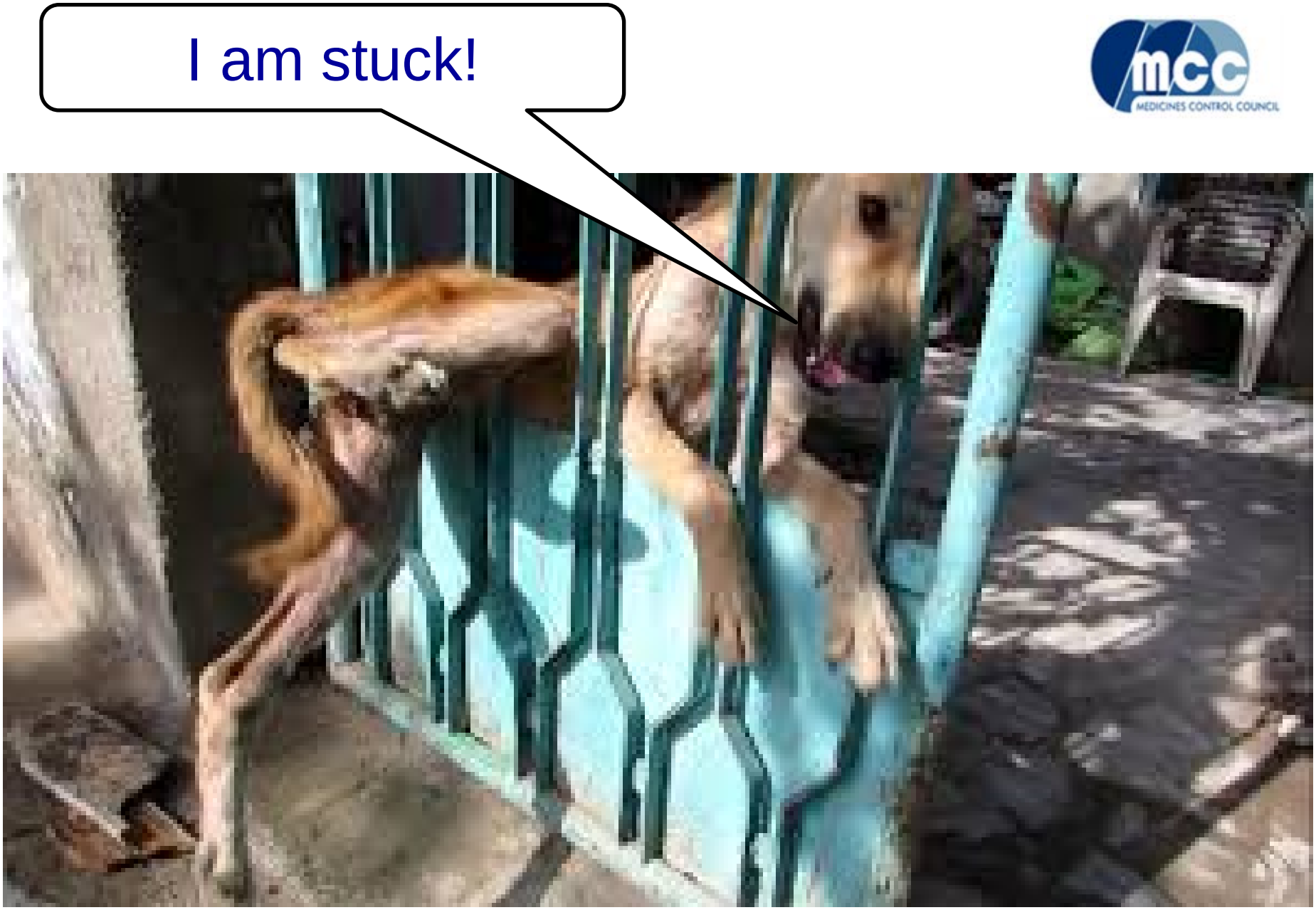
Bookmarks & Hyperlinks

Snip from amendment schedule

Response 3.5.1	Additional stability data has become available since the initial dossier submission. The updated stability summary (3.2.S.2.3.3.7.1 Stability Summary and Conclusions) and stability data (3.2.S.2.3.3.7.3 Stability Data) is provided with this response in support of the 60 month shelf-life originally requested.

Snip of what evaluator sees





So evaluation will stop!

Conclusion

Presentation and ***content*** issues in CTD manifest in eCTD

- **Check the submission**

Is this true?

- **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

For successful submissions

- Read & follow the guidelines
  - Remember Q&A
- Use the correct working code to prevent delays in process
  - 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
- Consider leaf titles in terms of the full life cycle of the product
- Don’t use abbreviations in leaf titles that are not generally recognised

For successful submissions *cont.*

- Use correct versions of 1.2.1 and validation template
- Ensure correct use of tabulated schedule of amendments (1.5.2.1)
- Check the view of 3.2.R
- Remember to disable thumbs.db
- Consider the presentation of the hard copy documents
- Check and do quality control
- Ask a colleague to check and navigate through the submission

Hyperlinks

Include at least the following hyperlinks:

- Cross-references in the **package insert** (1.3.1.1) to the actual references *(sequence 0000)*
  - *Where do the links go?*
- Cross-references in the **Patient Information Leaflet** (1.3.2) to the package insert (1.3.1.1) *(sequence 0000)*
- References in Sections B to D of the **Validation 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
- **Amendment Schedule** to the relevant documents

Bookmarks

- Provide enough bookmarks for easy navigation in the document
- Use meaningful names
- ToCs that are hyperlinked
- List of tables/figures if included
- Documents exceeding 5 pages that contain multiple headings/sections, tables, figures

Challenges

- Same reviewers as for paper submissions
  - Receive ca. 1 200 applications per year
- Expedited review (fast track) out of amended Medicines Act
  - eCTD used as alternative ?
- IT challenges e.g. internet bandwidth
- Local applicants don’t have software
- Misconceptions about eCTD
- Establishment of SAHPRA

MCC and Industry Partnership

Acknowledgements

- Evaluators
- Anita Smal – Abex Pharmaceutica, local Extedo partner
- Dr Silke Nolkemper & Christine Hirt, Extedo

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