ABEX
PHARMACEUTICA (PTY) LTD

eCTD : Industry Experience

SAPRAA - 26 March 2010

Anita Smal

Agenda

ABEX PHARMACEUTICA (PTY) LTD

- Introduction
- Experience with MCC pilot project
- Lessons learnt
- eCTD structure
- Life cycle
- Further guidance required from MCC
- Submission-ready documents
- Advantages of using eCTD software
- Conclusion

Introduction

ABEX PHARMACEUTICA (PTY) LTD

- ABEX Pharmaceutica offers marketing and technical services across the entire product value chain to the healthcare industry
- ABEX recognised the importance of the eCTD and became professional partners of Extedo
- Extedo is a leading supplier of electronic Regulatory Affairs solutions, eg eCTDmanager™
- eCTDmanager™ is an off-the-shelf scalable “all-in-one” electronic submission management solution for eCTD and non-eCTD electronic and paper submissions

Experience with MCC pilot project

ABEX PHARMACEUTICA (PTY) LTD

- Request from MCC for submissions in CTD and eCTD format – Dec 2009
- ABEX selected to submit eCTD
- A prototype eCTD was submitted with the assistance of Extedo, using eCTDmanager™

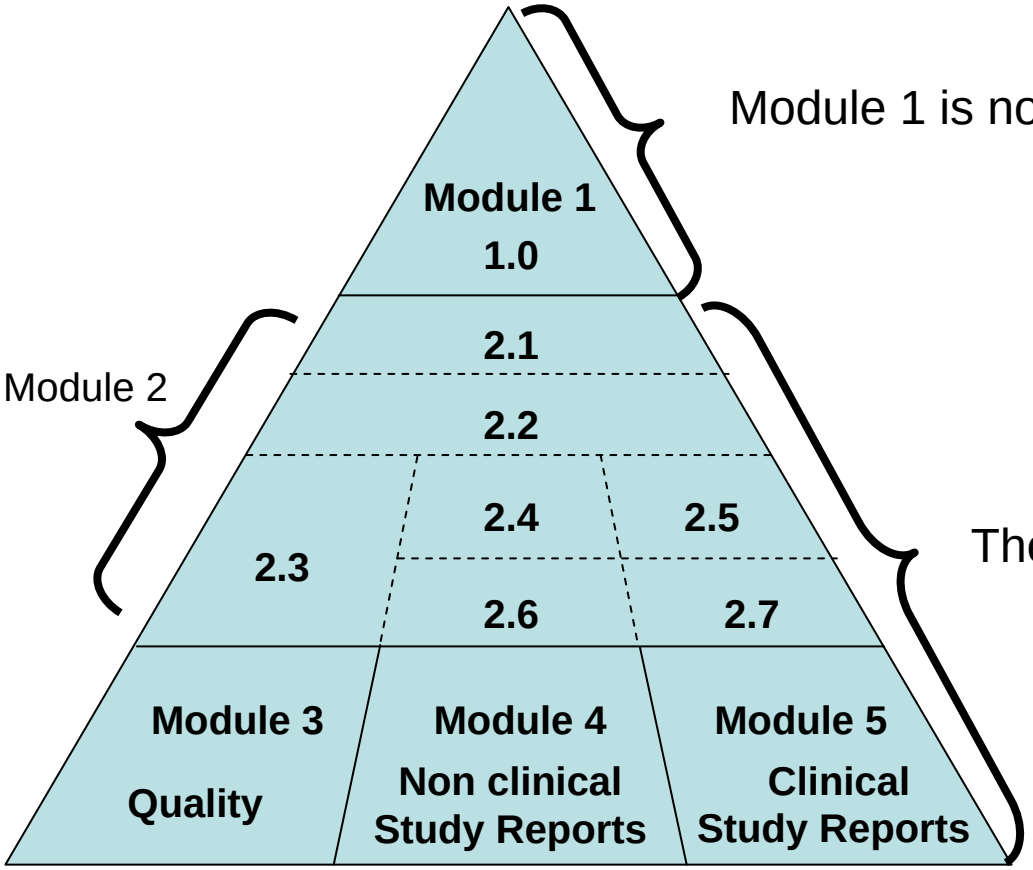
Lessons learnt

ABEX PHARMACEUTICA (PTY) LTD

- An eCTD is not just a collection of PDF's on a CD/DVD
- Further guidelines/information still required from MCC to enable submission of ZA eCTD's
- There is a lot that we can start doing to make the transition to CTD/eCTD easier

CTD structure

CTD = an appropriate format and organisation of data



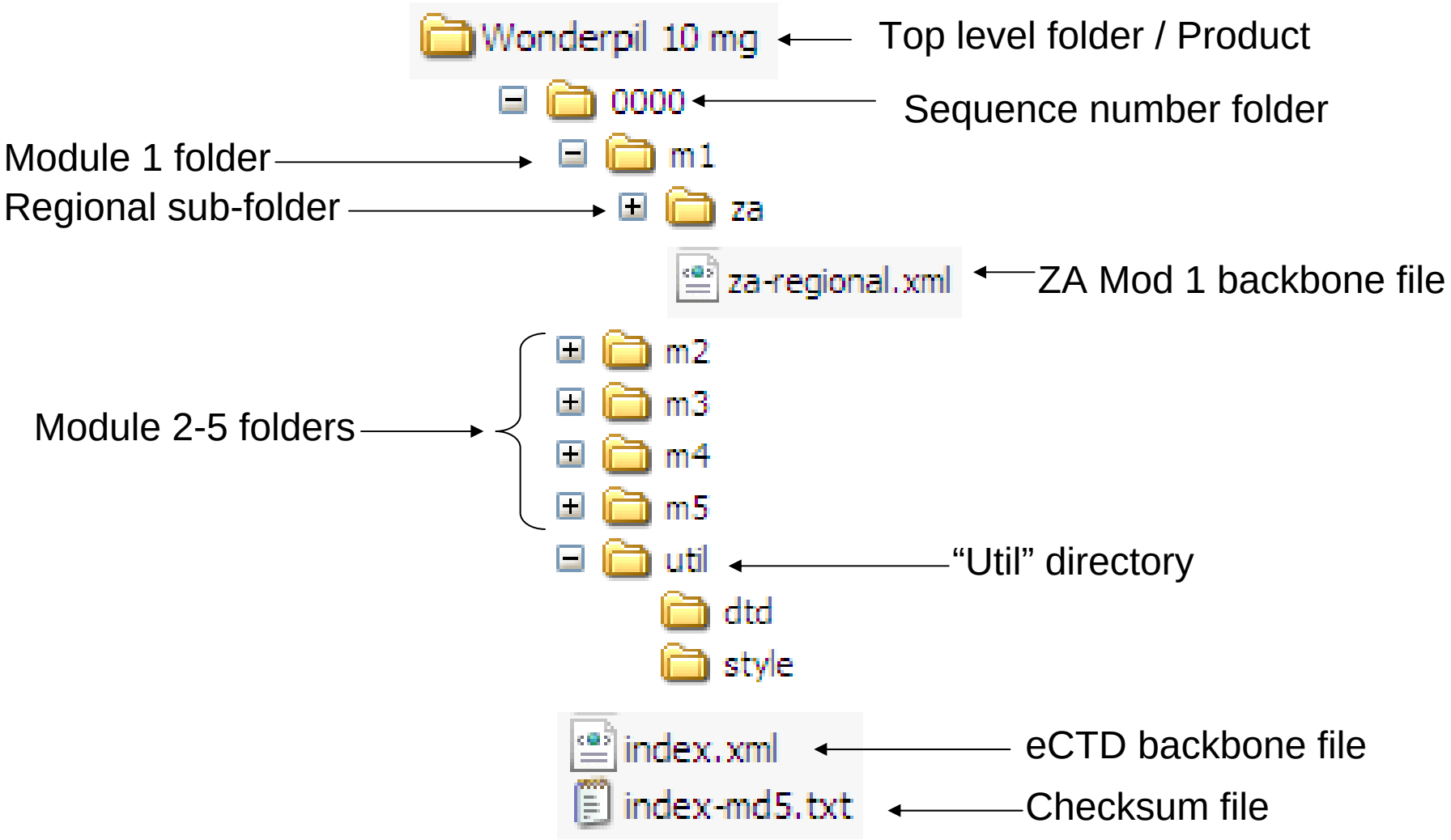
Module 1 is not part of the CTD

Module 2

The CTD

ZA Module 1 + Modules 2 to 5 = ZA CTD

eCTD structure



index.xml

ABEX PHARMACEUTICA (PTY) LTD

```
<m1-administrative-information-and-prescribing-information>
  <leaf ID="ID00008591" checksum="9302e6068bd169e1e5cfd0c38a4a1f3d" checksum-type="MD5" operation="new" xlink:href="m1/za/za-regional.xml">
    <title>za-regional.xml</title>
  </leaf>
</m1-administrative-information-and-prescribing-information>

<m2-common-technical-document-summaries>
  <m2-2-introduction>
    <leaf ID="ID00009063" application-version="PDF 1.4" checksum="37ac605081ed3f61203eea1a2809e947" checksum-type="MD5" operation="new"
        xlink:href="m2/22-intro/introduction.pdf">
      <title>2.2 Introduction</title>
    </leaf>
  </m2-2-introduction>
  <m2-3-quality-overall-summary>
    <m2-3-introduction>
      <leaf ID="ID00009064" application-version="PDF 1.4" checksum="d2ee68aba60a8ac730f04fe0a0e97eba" checksum-type="MD5" operation="new"
          xlink:href="m2/23-qos/introduction.pdf">
        <title>2.3 Introduction</title>
      </leaf>
    </m2-3-introduction>
    <m2-3-s-drug-substance manufacturer="Wizard Ltd" substance="Wonderdrug" xml:lang="en">
      <leaf ID="ID00009065" application-version="PDF 1.4" checksum="ba0c8b7f51fb75ec4056f0380f09110d" checksum-type="MD5" operation="new"
          xlink:href="m2/23-qos/drug-wonderdrug-wizardltd.pdf">
        <title>2.3.S Active Pharmaceutical Ingredient</title>
      </leaf>
    </m2-3-s-drug-substance>
    <m2-3-p-drug-product dosageform="Film-coated tablets" manufacturer="Miracle Co" product-name="Wonderpil 10 mg" xml:lang="en">
      <leaf ID="ID00008968" application-version="PDF 1.4" checksum="f5970733466f6792d0492a4ae12b6488" checksum-type="MD5" operation="new"
          xlink:href="m2/23-qos/miracleco-wonderpil10mg-filmcoatedtablets.pdf">
        <title>2.3.P Finished Pharmaceutical Product</title>
      </leaf>
    </m2-3-p-drug-product>
    <m2-3-a-appendices>
      <leaf ID="ID00009066" application-version="PDF 1.4" checksum="e2c325acb268cca16acb59abc37d23c1" checksum-type="MD5" operation="new"
          xlink:href="m2/23-qos/appendices.pdf">
        <title>2.3.A Appendices</title>
      </leaf>
    </m2-3-a-appendices>
```

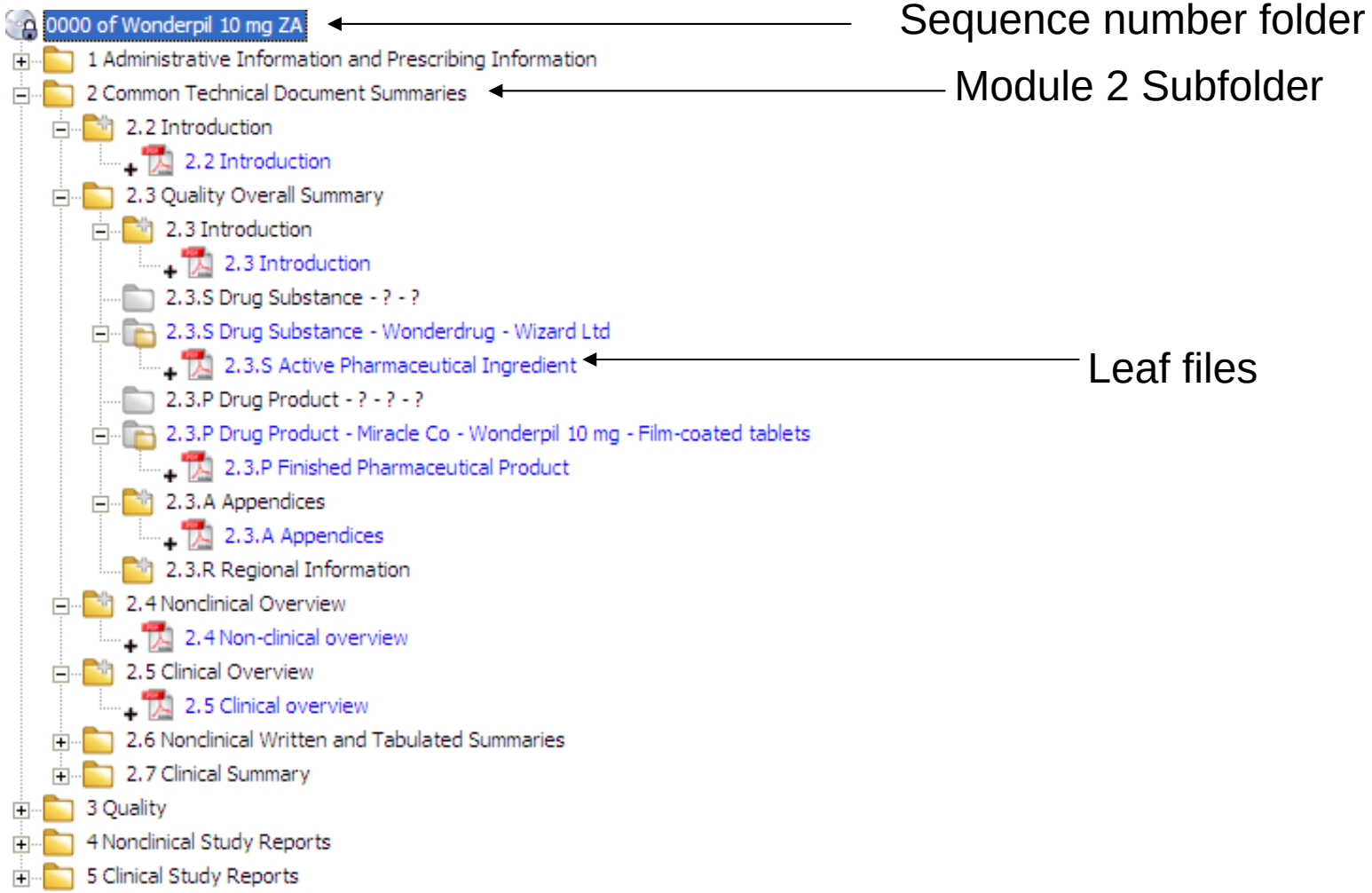
index.xml

ABEX PHARMACEUTICA (PTY) LTD

eCTD DTD version 3.2

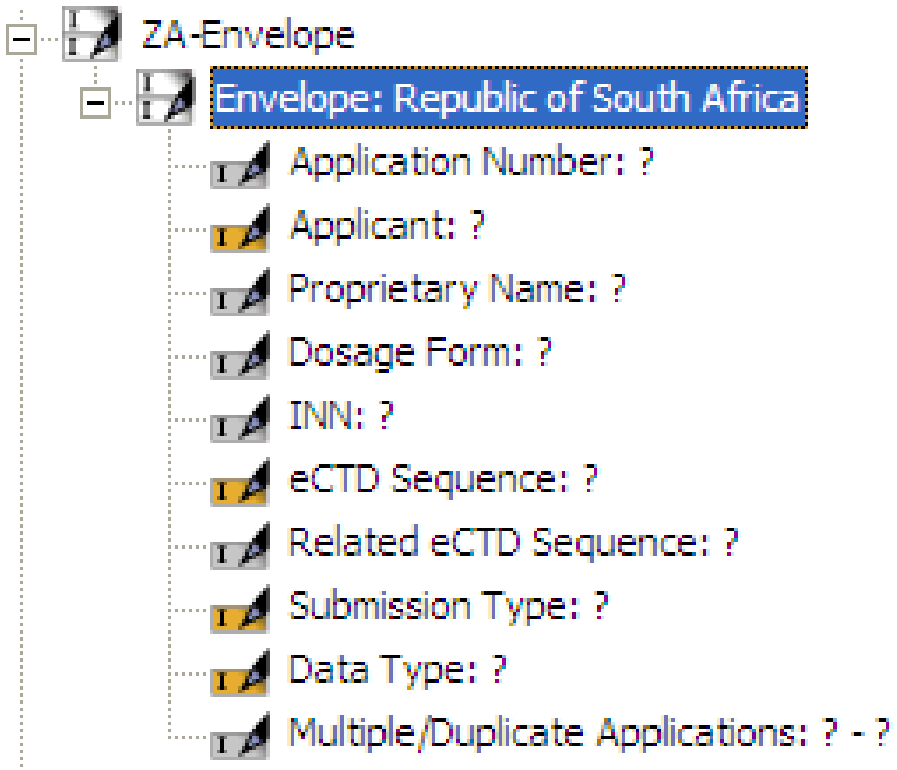
- m1-administrative-information-and-prescribing-information
  - za-regional.xml [new]
- m2-common-technical-document-summaries
  - m2-2-introduction
    - 2.2 Introduction [new]
  - m2-3-quality-overall-summary
    - m2-3-introduction
      - 2.3 Introduction [new]
    - m2-3-s-drug-substance [manufacturer: Wizard Ltd] [substance: Wonderdrug]
      - 2.3.S Active Pharmaceutical Ingredient [new]
    - m2-3-p-drug-product [manufacturer: Miracle Co] [product name: Wonderpil 10 mg] [dosage form: Film-coated tablets]
      - 2.3.P Finished Pharmaceutical Product [new]
    - m2-3-a-appendices
      - 2.3.A Appendices [new]
  - m2-4-nonclinical-overview
    - 2.4 Non-clinical overview [new]
  - m2-5-clinical-overview
    - 2.5 Clinical overview [new]

eCTD structure



A portion of the eCTD structure as seen using an XML viewing tool

Envelope



- Metadata
- Indicates relationships between sequences for effective life cycle management

Life cycle

ABEX PHARMACEUTICA (PTY) LTD

- eCTD life cycle is the management of all regulatory activities for a specific product from the initial submission, through pre-registration responses to committee recommendations, and post-registration amendments
- Intention to maximise re-use of information and minimise re-submission of documents
- Only changes are submitted – the first eCTD sequence can be referenced throughout the product life cycle

Life cycle

ABEX PHARMACEUTICA (PTY) LTD

1 **In Submission 0000 add a document:**

NEW Document*:* Each Document added in 0000 submission is NEW

2 **In Submission 0001 and the following**

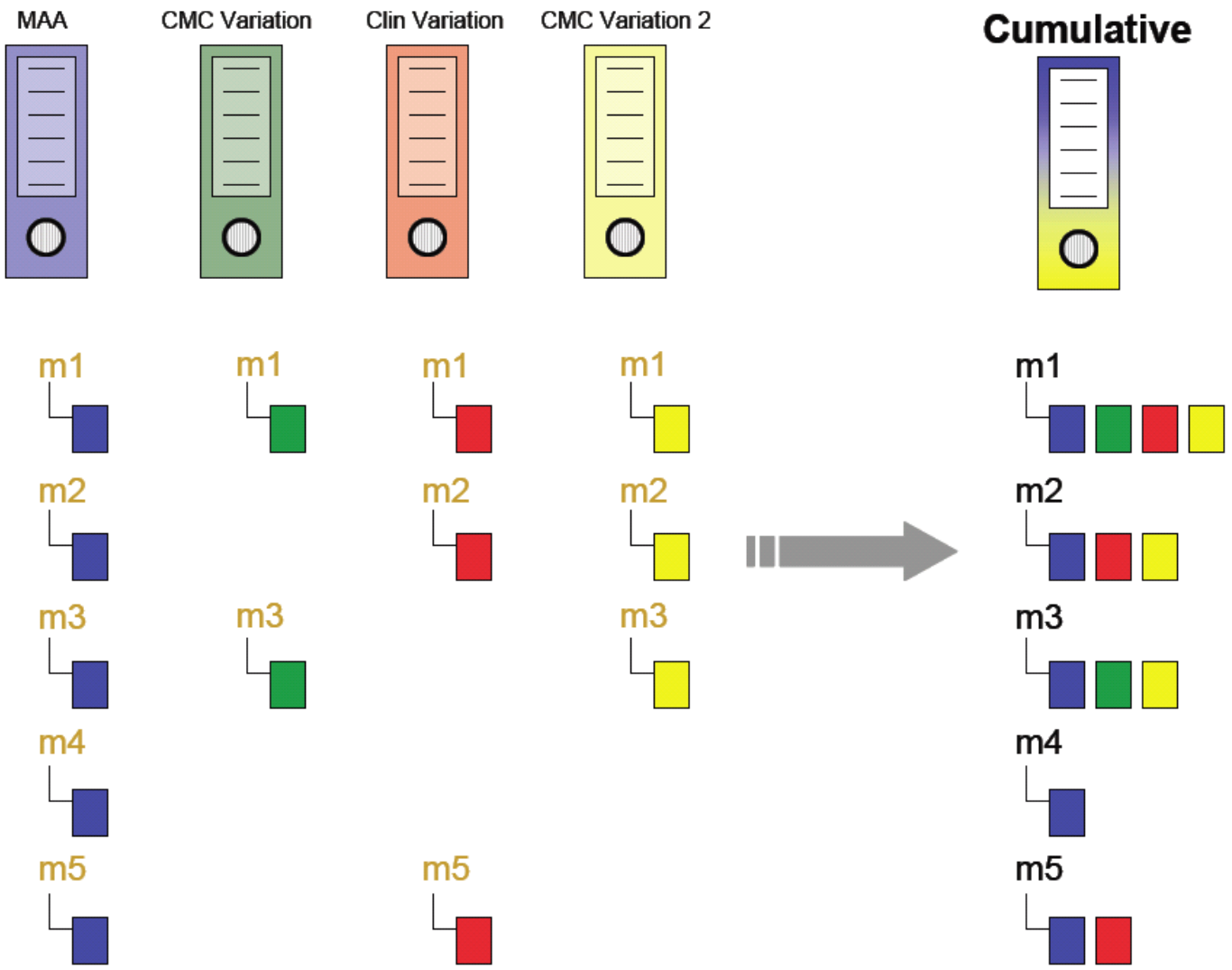
DELETE Document: The document was added in submission 0000 and deleted in submission 0001

REPLACE Document: The document is replaced in submission 0001

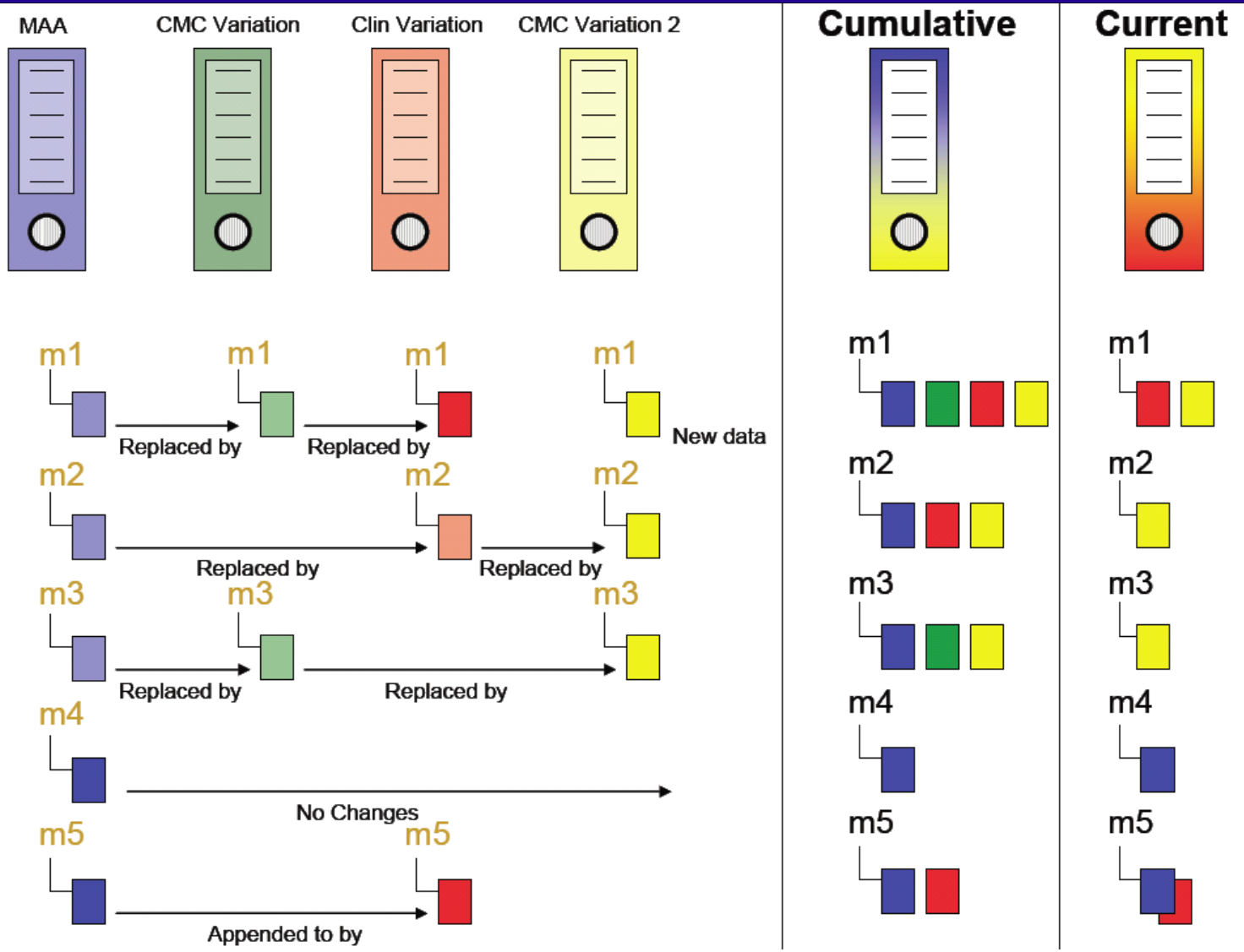
APPEND Document: The document is appended in submission 0001

NEW Document: The document is added to the current submission for the first time.

Life cycle


MAA
CMC Variation
Clin Variation
CMC Variation 2
Cumulative
m1
m2
m3
m4
m5
m1
m3
m1
m2
m5
m1
m2
m3
m1
m2
m3
m4
m5

Life cycle


MAA
CMC Variation
Clin Variation
CMC Variation 2
Cumulative
Current
m1
Replaced by
New data
m2
m3
m4
No Changes
m5
Appended to by

Further guidance required

ABEX PHARMACEUTICA (PTY) LTD

- South African Module 1 Specification for eCTD
  - File formats
  - Use of electronic signatures
  - Use of links
  - Handling of empty or missing eCTD sections
  - General architecture of Module 1
  - Envelope
  - Directory/file structure for Module 1
  - ZA Regional DTD

Further guidance required

ABEX PHARMACEUTICA (PTY) LTD

- South African eCTD Validation Criteria
  - Technical validation vs Content Validation
  - Error classification
  - Validation process
  - Technical validation criteria
  - Test submissions

Further guidance required

ABEX PHARMACEUTICA (PTY) LTD

- Guidance on providing regulatory information in eCTD format
  - Structure and content
  - Submission media
  - File naming conventions
  - How to handle additional files in MS Word format
  - Virus check
  - Life cycle management
  - Baseline submissions
  - Test submissions?
  - Where and how to submit

Submission ready documents

ABEX PHARMACEUTICA (PTY) LTD

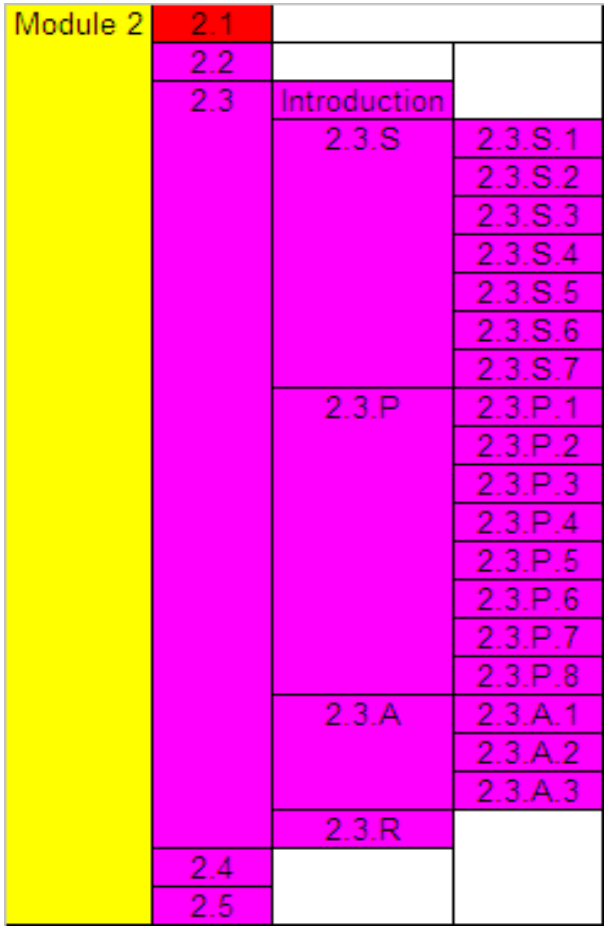
- Content meets current requirements
- Correct granularity
- Correct layout, standards, styles
- Intelligent PDF's
- Use of templates
  - Improved quality & consistency
  - Comply with eCTD specifications
  - Can spend more time on content and less on formatting

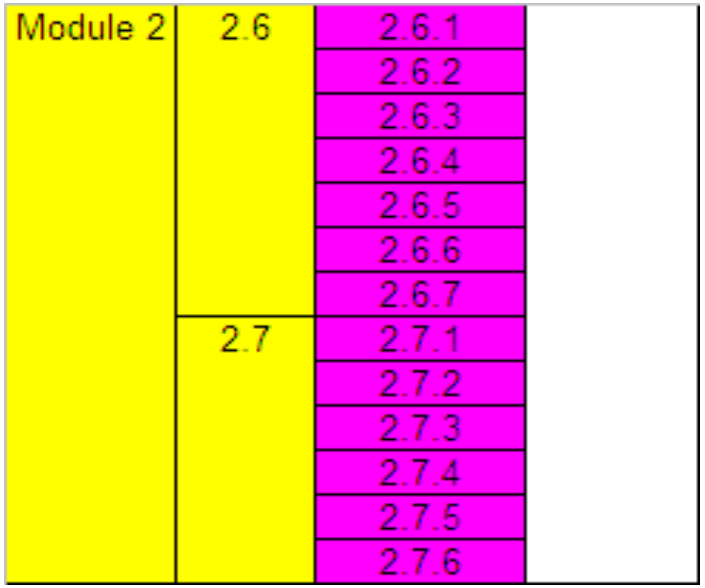
Granularity

ABEX PHARMACEUTICA (PTY) LTD

- A document is defined for a paper submission as a set of pages, numbered sequentially and divided from other documents by a divider
- A document can be equated to a file for an electronic submission.
- The granularity of the paper and electronic submissions should be equivalent.
- Once a particular granularity has been adopted, the same granularity should be used throughout the life of the dossier
- The following tables describe the levels in the CTD/eCTD hierarchy at which documents/files should be placed and whether single or multiple documents are appropriate at each point.

Granularity: Module 2





Documents rolled up to this level are not considered appopriate

One or multiple documents can be submitted at this level

Granularity: Module 3

Module 3	3.1			
	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.3.3
			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

Module 3	3.2	3.2.P	3.2.P.1	
			3.2.P.2	3.2.P.2.1
				3.2.P.2.2
				3.2.P.2.3
				3.2.P.2.4
				3.2.P.2.5
				3.2.P.2.6
			3.2.P.3	3.2.P.3.1
				3.2.P.3.2
				3.2.P.3.3
				3.2.P.3.4
				3.2.P.3.5
			3.2.P.4	3.2.P.4.1
				3.2.P.4.2
				3.2.P.4.3
				3.2.P.4.4
				3.2.P.4.5
				3.2.P.4.6
			3.2.P.5	3.2.P.5.1
				3.2.P.5.2
				3.2.P.5.3
				3.2.P.5.4
				3.2.P.5.5
				3.2.P.5.6
			3.2.P.6	
			3.2.P.7	
			3.2.P.8	3.2.P.8.1
				3.2.P.8.2
				3.2.P.8.3
		3.2.A	3.2.A.1	
			3.2.A.2	
			3.2.A.3	
		3.2.R	Refer to regional guidance	
	3.3	One file per reference		

Documents rolled up to this level are not considered appopriate

One or multiple documents can be submitted at this level

Granularity: Module 4

Module 4	4.1				
	4.2	4.2.1	4.2.1.1	Studies	
			4.2.1.2	Studies	
			4.2.1.3	Studies	
			4.2.1.4	Studies	
		4.2.2	4.2.2.1	Studies	
			4.2.2.2	Studies	
			4.2.2.3	Studies	
			4.2.2.4	Studies	
			4.2.2.5	Studies	
			4.2.2.6	Studies	
			4.2.2.7	Studies	
		4.2.3	4.2.3.1	Studies	
			4.2.3.2	Studies	
			4.2.3.3	4.2.3.3.1	Studies
				4.2.3.3.2	Studies
			4.2.3.4	4.2.3.4.1	Studies
				4.2.3.4.2	Studies
				4.2.3.4.3	Studies
			4.2.3.5	4.2.3.5.1	Studies
				4.2.3.5.2	Studies
				4.2.3.5.3	Studies
				4.2.3.5.4	Studies
			4.2.3.6	Studies	
			4.2.3.7	4.2.3.7.1	Studies
				4.2.3.7.2	Studies
				4.2.3.7.3	Studies
				4.2.3.7.4	Studies
				4.2.3.7.5	Studies
				4.2.3.7.6	Studies
				4.2.3.7.7	Studies
	4.3	One file per reference			

Documents rolled up to this level are not considered appopriate

One or multiple documents can be submitted at this level

Granularity: Module 5

Module 5	5.1			
	5.2			
	5.3	5.3.1	5.3.1.1	Studies
			5.3.1.2	Studies
			5.3.1.3	Studies
			5.3.1.4	Studies
		5.3.2	5.3.2.1	Studies
			5.3.2.2	Studies
			5.3.2.3	Studies
		5.3.3	5.3.3.1	Studies
			5.3.3.2	Studies
			5.3.3.3	Studies
			5.3.3.4	Studies
			5.3.3.5	Studies
		5.3.4	5.3.4.1	Studies
			5.3.4.2	Studies
		5.3.5	5.3.5.1	Studies
			5.3.5.2	Studies
			5.3.5.3	Studies
			5.3.5.4	Studies
		5.3.6		
		5.3.7	Studies	
	5.4	One file per reference		

Documents rolled up to this level are not considered appopriate

One document can be submitted at this level

One or multiple documents can be submitted at this level

General considerations

ABEX PHARMACEUTICA (PTY) LTD

- Fonts: Times New Roman or Arial
- Font size:
  - 12 point – narrative text
  - 10 point in tables and footnotes
- Colour:
  - Black font recommended
  - Avoid shading and background shadowing
- Hyperlinks
  - Blue text or rectangles using thin lines

General considerations

ABEX PHARMACEUTICA (PTY) LTD

- Page size: A4 (210 x 297 mm)
- Margins: At least 2,5 cm on left side
- Headers and footers: unique header or footer that briefly identifies subject matter
- Page numbering: page numbers for the document and PDF file should be the same, start at 1 and number consecutively
- Page orientation: portrait pages should be portrait and landscape should be landscape prior to saving PDF document in final form

General considerations

ABEX PHARMACEUTICA (PTY) LTD

- PDF's
  - Don't use password protection / security
  - Intelligent PDF's where possible
    - Bookmarks from each item listed in the ToC
    - Hyperlinks
  - Avoid scanning where possible
    - If you have to scan, scan at resolution of 300 dpi
    - Don't use greyscale or colour
    - OCR where possible
    - Correct granularity
  - Open dialog box: set initial view to *Bookmarks* and *Page*
  - PDF version 1.4
  - Max file size 100 MB
  - Optimise for fast web view

Advantages using eCTDmanager™

ABEX PHARMACEUTICA (PTY) LTD

- Users don’t need any knowledge of XML technology.
- Supports various submission structures eg CTD, eCTD, NeeS, and other
- Electronic and paper compliant submissions
- User friendly
- Structural elements can be added, edited and deleted.
- Documents can be scanned, copied, moved or imported from the file system or from most Document Management Systems (DMS).
- Powerful hyperlinking engine
- It takes care of file and folder names and PDF versions
- An integrated validation function ensures compliance of the generated submission to ICH and regional specifications.

Conclusion

ABEX PHARMACEUTICA (PTY) LTD

There is a lot that we can do in preparation for eCTD…

…. to ensure a painless transition from paper MBR1 / MRF1 / CTD to eCTD

References

- Extedo Ltd
- South African CTD; MCC Edition Nov 2009
- Guidance for the submission of the SA CTD/eCTD Module 1; 2 00 Guidance Module 1 v1_3 working document.doc
- ICH eCTD Specification V 3.2.2; 16 July 2008
- ICH Organisation of the CTD for the Registration of Pharmaceuticals for Human Use M4, 13 Jan 2004
- Swiss Module 1 Specification for eCTD, Version 1.01.1
- Swissmedic Guidance for Industry on Providing Regulatory Information in eCTD Format; Version 1.0
- Swiss eCTD Validation Criteria; Version 1.0