BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

General aspects

Session: Going digital (7 May 2013, 11:15–12:45)
Presented by: Klaus Menges (BfArM), Olivier Simoen (EMA)

Version 01.01

EU 28: science, medicines, health
A regulatory system fit for the future
6–7 May 2013, Dubrovnik, Croatia

Overview

- eCTD and NeeS
- Technical validation
- eCTD CMDh best practice guide
- Process from submission to publication

NeeS in practice

m1-toc.pdf - Adobe Acrobat Pro

Datei Bearbeiten Anzeige Dokument Kommentare Formulare Werkzeuge Erweitert Fenster Hilfe

Erstellen Zusammenführen Zusammenarbeiten Schützen Unterschreiben Formulare Multimedia Kommentar

1 / 3 113% Suchen

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1 Administrative Information and Prescribing Information
1 TOC
Module 1 EU
1.0 Cover letter
Germany
com

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de-form-6.0mg.doc
Netherlands
nl-form-1.5mg.doc
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nl-form-4.5mg.doc
nl-form-6.0mg.doc
1.3 Product Information
1.3.1 SPC, Labelling and Package Leaflet
Common: Summary of Product Characteristics: English
m1-3-1-common.doc
1.3.1 PIM
1.3.2 Mock-up
Common

ctd-toc.pdf - Adobe Acrobat Pro

Datei Bearbeiten Anzeige Dokument Kommentare

Erstellen Zusammenführen

MODULE 1.1 COMPRE

MODULE

1.1

MODULE

2.1

MODULE

3.1

MODULE

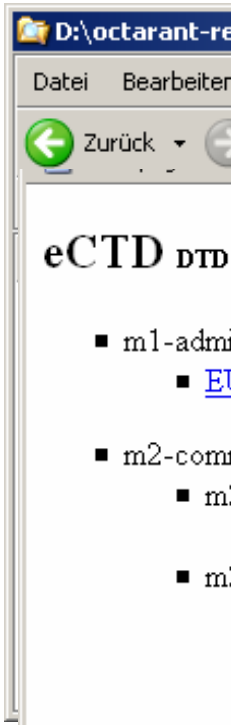
4.1

MODULE

5.1

auf der
auf der
auf der

eCTD in practice



EU Module 1

DTD version 1.4

Envelope for SK

Submission:	Type: Initial Marketing Authorisation
	Number: SK/H/0120/001-002-003
Tracking Number(s):	to be advised
Applicant:	KRKA
Agency:	Slovak Rep - State Institute for Drug Control (SK-SIDC)
Procedure:	Decentralised Procedure (DCP)
Invented Name:	MIR… …nim, MIROP 4 mg tablety s predĺženým uvoľňovaním, MIROP 8 mg tablety s predĺženým uvoľ…
INN:	ROP…
Sequence:	0005
Related Sequence:	
Submission Description:	SK/H…

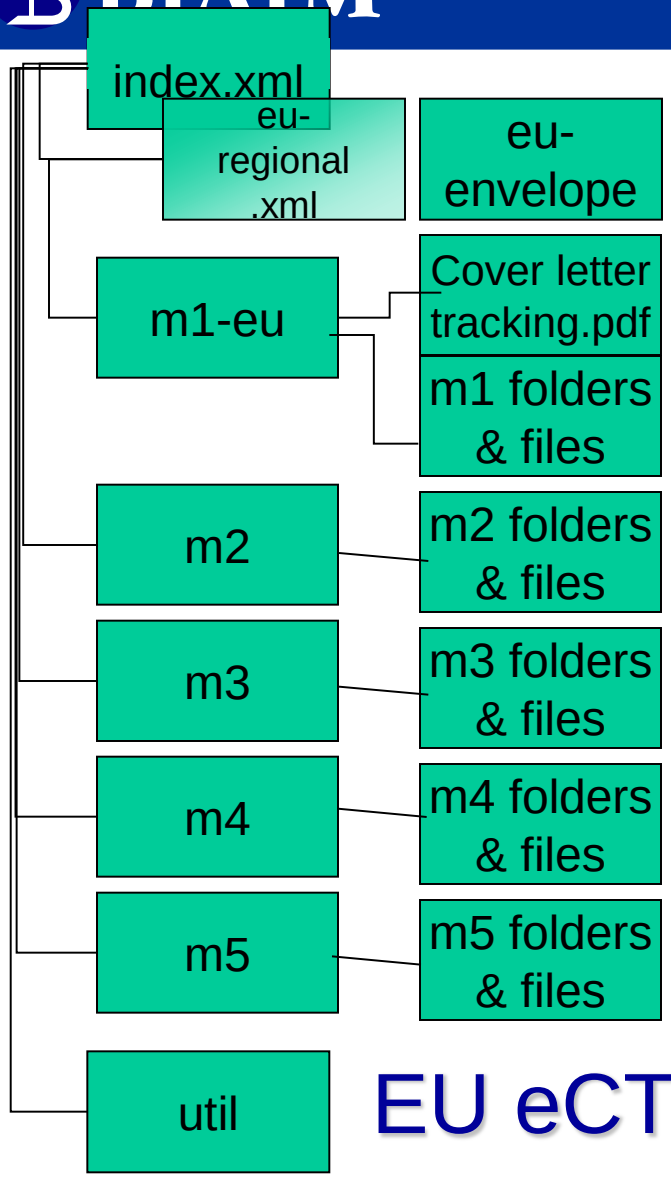
Envelope for IT

Submission:	Type: Initial Marketing Authorisation
	Number: SK/H/0120/001-002-003
Tracking Number(s):	to be advised
Applicant:	KRKA
Agency:	Italy - Agenzia Italiana del Farmaco (IT-AIFA)
Procedure:	Decentralised Procedure (DCP)
Invented Name:	MIROP, MIROP, MIROP
INN:	ROPINIROLE HYDROCHLORIDE
Sequence:	0005
Related Sequence:	
Submission Description:	SK/H/0120/001-002-003 - integrated dossier

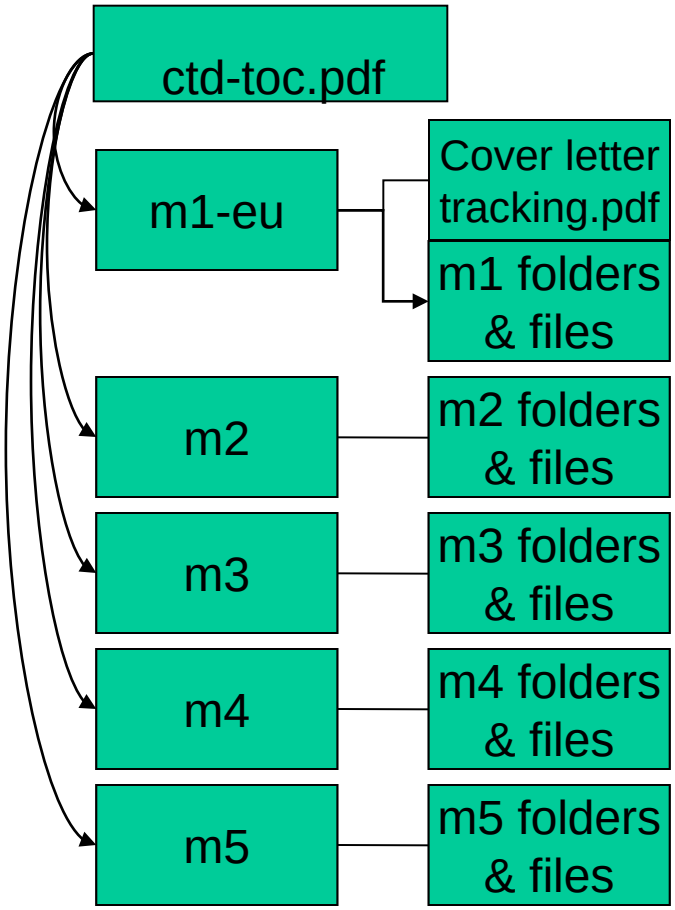
Envelope for NO

Submission:	Type: Initial Marketing Authorisation
	Number: SK/H/0120/001-002-003

- Stability - Substance 1, Manufacturer 1 [new]
- m2-3-s-drug-substance [manufacturer: Manufacturer 2] [substance: Substance 2]
  - General Information - Substance 2, Manufacturer 2 [new]



EU eCTD

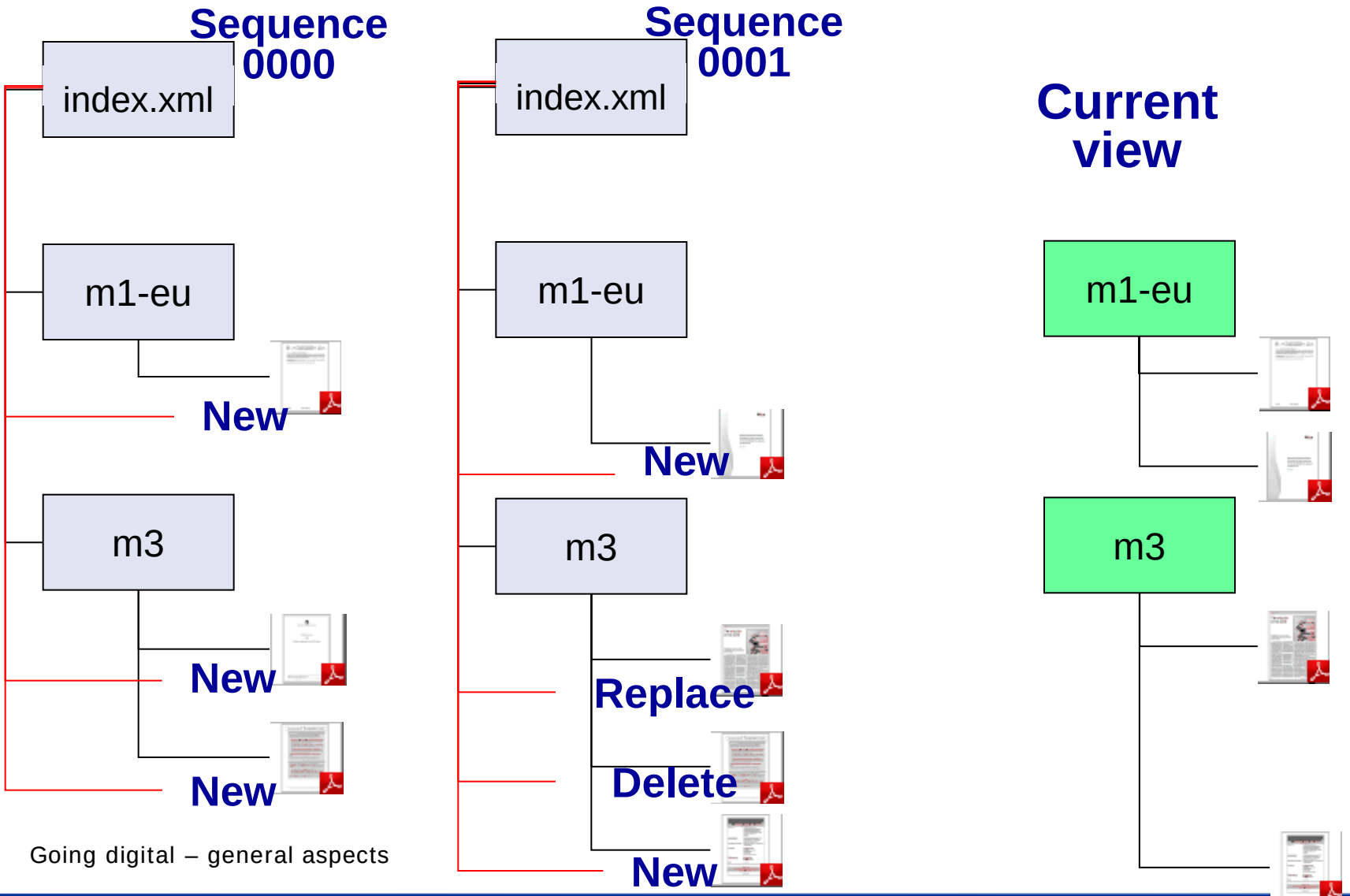


EU NeeS

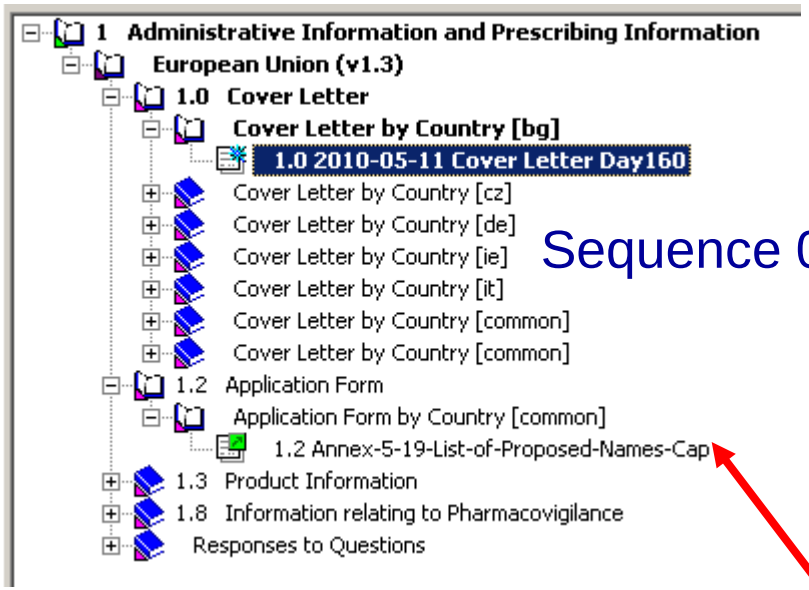
outside eCTD
working documents Word files

"outside" NeeS
working documents Word files

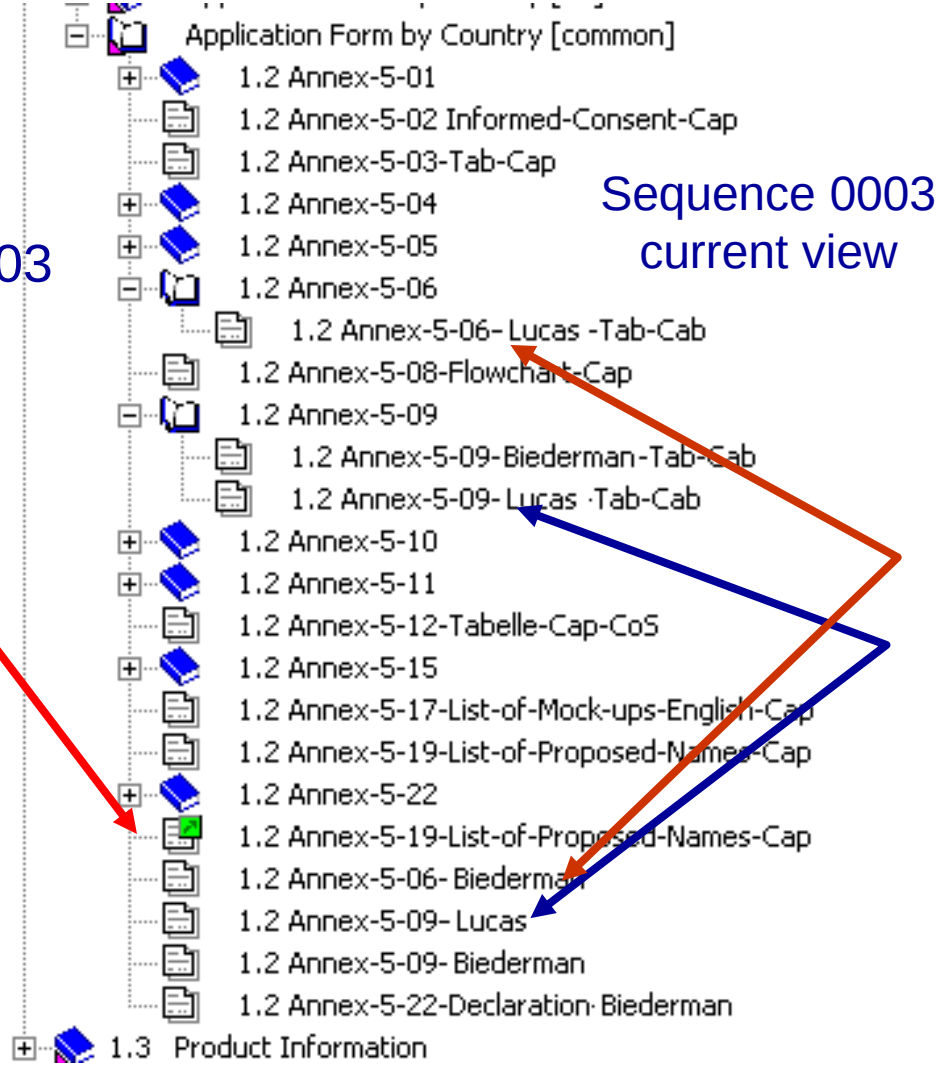
eCTD lifecycle management



Problems with LCM operators



Sequence 0003



Sequence 0003 current view

Errors:

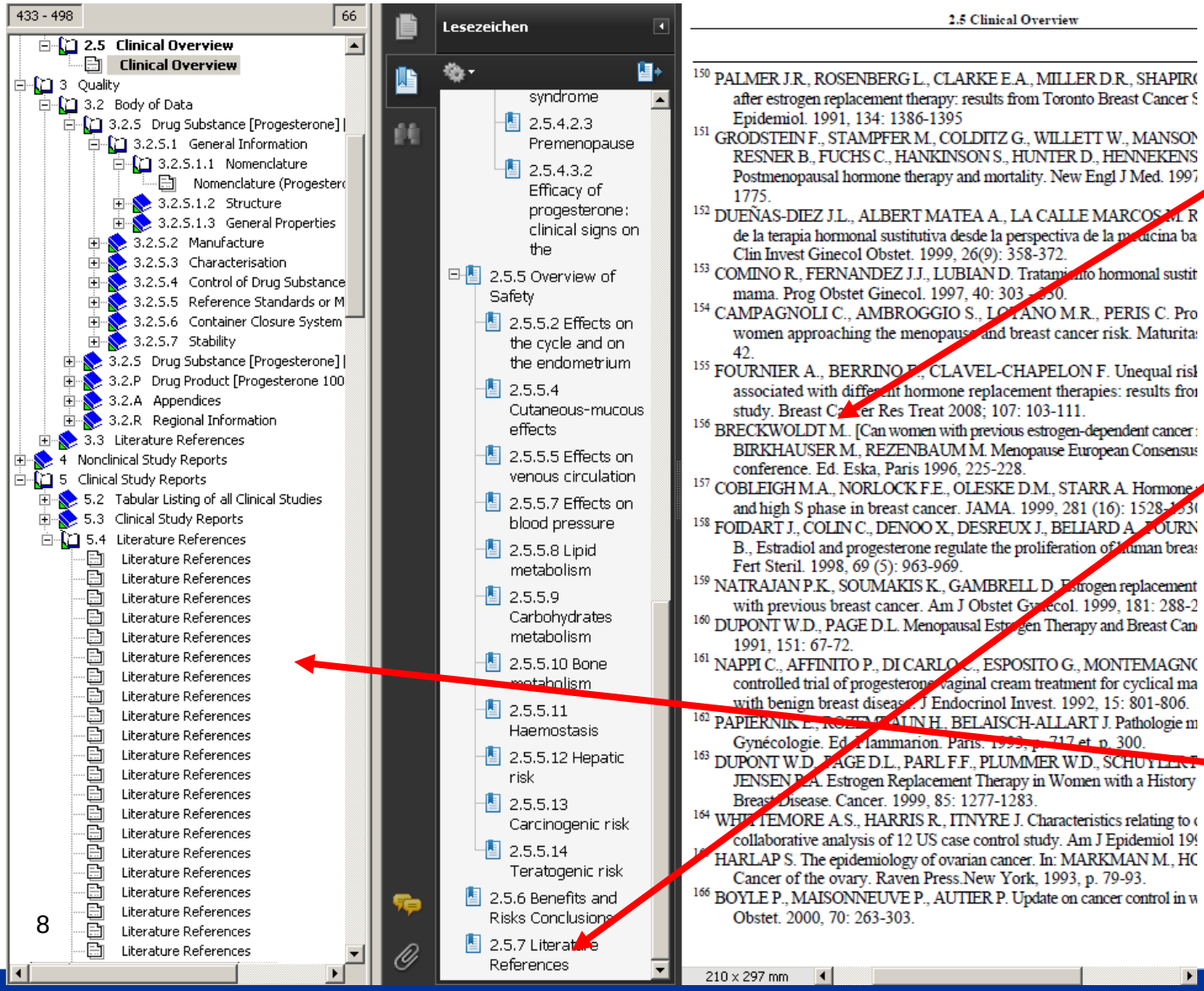
- New annex 5-19 listed under 5-22, replace not performed
- Annex 5-06 wrongly listed under 5-22
- Added annexes 5-09 wrongly listed under 5-22

Problems with pdf quality

- Incorrect pdf versions (only in case of version 1.3 or below)
- Missing bookmarks
- Meaningless named bookmarks
- Broken hyperlinks within sequences or across sequences
- Huge pdf files, especially if unstructured
- Scanned images and therefore no text search possible
- Badly readable paper copies badly scanned

All of those we want to have less of

Deficits in supporting navigation



Long list of references, title accessible by links within the document

Bookmark points to the section only

TOC is not helpful

Quality of pdf–Files

container-closure-system.pdf - Adobe Acrobat Professional

Datei Bearbeiten Anzeige Dokument Kommentare Formulare Werkzeuge Erweitert Fenster Hilfe

PDF erstellen | Dateien zusammenführen | Exportieren | Schützen | Unterschreiben | Formulare | Überprüfen und kommentieren

Lesezeichen

Optionen

Missing bookmarks, navigation not supported

Module 3.2.P.7	**Container closure system**
Module 3.2.P.7.1	**Peelable lidding foil and PVC film**
Page 1 of 33	**March 2010**

P.7. CONTAINER CLOSURE SYSTEM

P.7.1 PEELABLE LIDDING FOIL AND PVC FILM

Packing material	Supplier
228 mm, Peelable lidding foil	Acare Packaging
234 mm, PVDC coated PVC clear film	Bcare Limited

❖ **Technical data for the container closure system:**

228 mm, Peelable lidding foil – Acare Packaging

- Test Specification - Finished product manufacturer
- Certificate of analysis - Finished product manufacturer
- Certificate of analysis – Acare packaging
- Technical data sheet – Acare packaging
- Clearance certificate for Pin Pharma - Statement of compliance with EU regulations – Acare packaging
- Statement for absence of Pin holes – Acare packaging

234 mm, PVDC coated PVC clear film – Bcare Limited

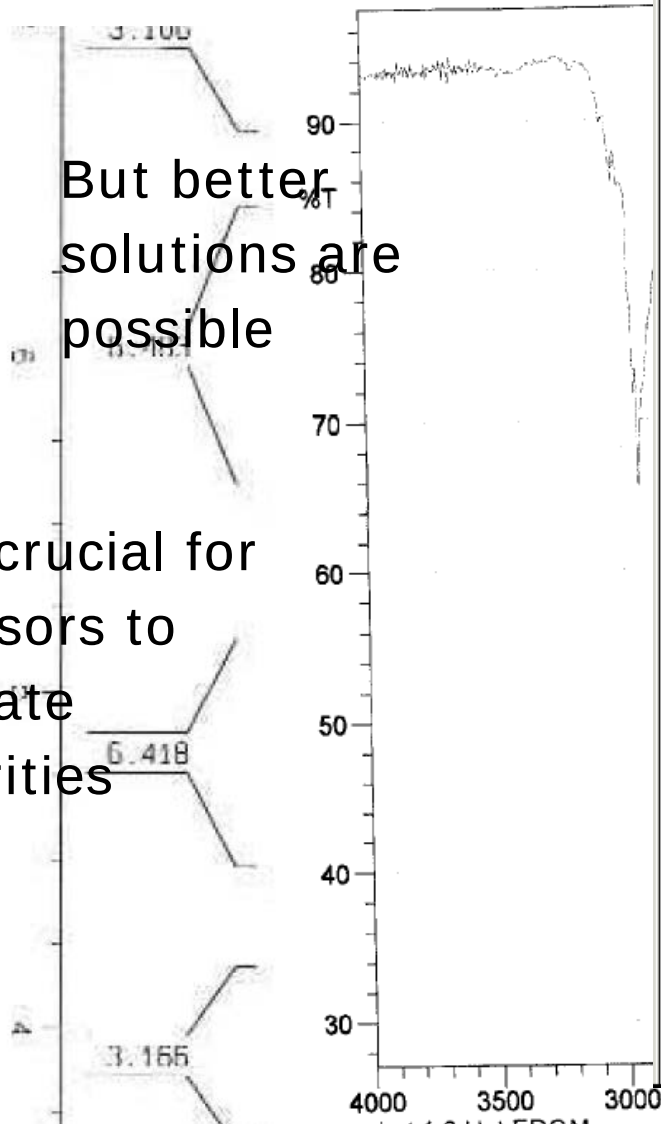
- Test Specification - Finished product manufacturer
- Technical specification – Bcare Limited
- Certificate of analysis - Finished product manufacturer
- Certificate of analysis – Bcare Limited

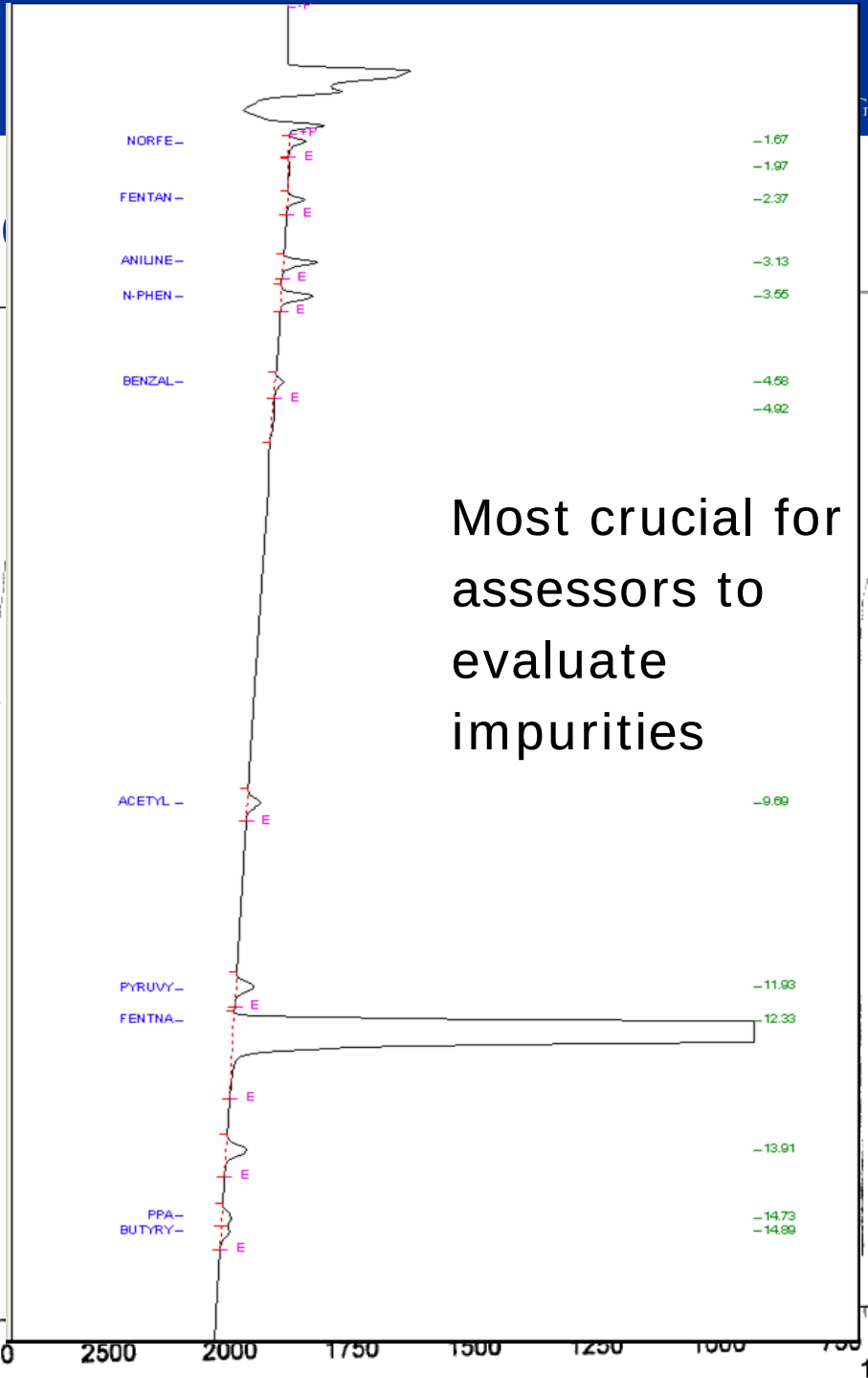
9.4.7 Prior and concomitant therapy 0019

Most Frequent Probl

But better solutions are possible

Most crucial for assessors to evaluate impurities





Most crucial for assessors to evaluate impurities

Current recommendations for e-submissions of full dossiers

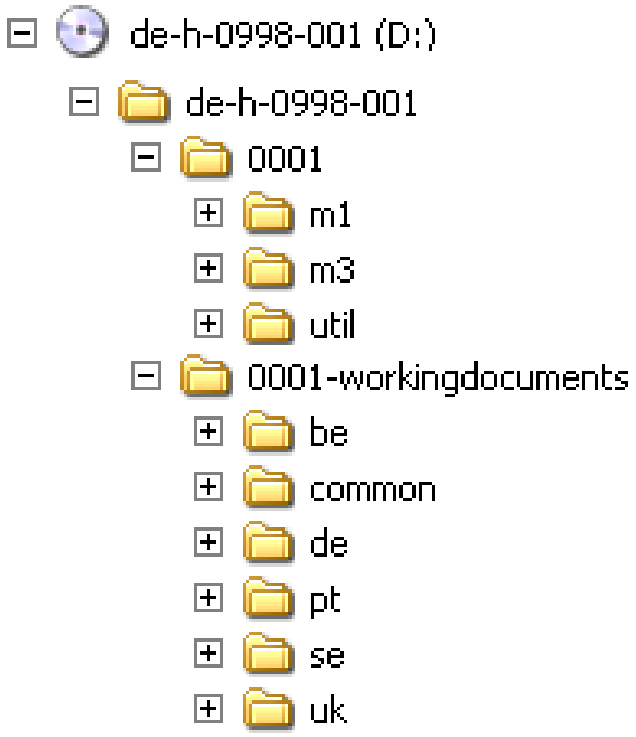
- TIGes: Non-eCTD e-submission (NeeS) as a transition step to eCTD compliance (version 3.0)
- TIGes: eCTD submission as the „new“ standard will detail business process aspects and requirements (version 2.0)
- TIGes: eCTD / NeeS – Technical Validation Criteria (current versions 4.1 and 3.0, new versions 5.0 / 4.0 by Sept 1, 2013)
- CMDh: Best Practice Guide on the Use of the Electronic Common Technical Document (eCTD) in the Mutual Recognition and Decentralised Procedures (version 3.0)
- NtA/CMDh: Requirements on Electronic submissions for new applications, variations, and renewals within MRP, DCP or National procedures (regulary updates published)
- EMA: Q&A on Implementation of Electronic-only Submission and eCTD Submission

Folder structure required

- Structured in accordance with CTD (NeeS) or completely in accordance with ICH specifications on m2 to m5 and EU specification on m1 (eCTD)
- Breakdown in conformity with the ICH Granularity Document
- Root directory named by product name or procedure number
- Working documents always in a separate folder on root level named <sequence>-workingdocuments

Note

- Do not use container (e.g. zip, rar, 7z) for submissions on CD or DVD



File formats

General

- In accordance with ICH and EU eCTD specifications
- PDF not below version1.4, versions 1.5, 1.6 and 1.7 are accepted as well
- XML in Module 1 allowed, e.g. application form

Portable Document Format (PDF)

- Generated from electronic source documents
- Module 2 always from an electronic source document
- Scanned for certain documents only
- Scan resolution about 300 dpi recommended

BfArM

Sending Electronic M

Address

Template of cover letter to be sent to BfArM

<Applicant>
<Address>
<Address>
<Post code> <Town>
<Country>

<Refe

<National Agency>
<Address>
<Address>
<Post code> <Town>
<Country>

e-only
submissio

Subject: Submission of Application Dossier(s) for <Product Name(s) in the MS where the appl is submitted> <MPR / DCP-Procedure Number(s), <ENR>>

Dear Sirs,

We are pleased to submit our Application Dossier(s) for a <Mutual Recognition> / <Decentr Procedure which details are as follows:

Name of the medicinal product(s) (in the RMS): ....
Pharmaceutical form(s) and strength(s): ... ...
INN/active substance(s):... ... ... **ATC Code(s):** ....

Legal Basis of the Application(s): ....
When appropriate, please indicate:
- Use of European Reference Medicinal Product ....
- If the strength(s) of the Reference MP differs between RMS/CMS ☐ Yes ☐
- If the pharmaceutical form(s) of the Reference MP differs between RMS/CMS ☐ Yes ☐
- If the indication(s) of the Reference MP differs between RMS/CMS ☐ Yes ☐

Technical validation…

Will also include for PDF files:

- Check of security settings
  No restrictions allowed for password, copy & paste, print
- Whether hyperlinks and bookmarks are functional
- Maximum file size 100 MB
- Path length (starting at sequence level)
  Too long path lengths can easily be avoided

- Existence of ctd-toc.pdf and mX-toc.pdf as appropriate (NeeS only)
  You may use the NeeS TOC Builder

Main Principles of Technical Validation

- Two levels of tests:
  - Pass/Fail
  - Best Practice (warnings)
  - No other or additional criteria should be set by any agencies for technical validation
- If other checks are needed, these should be proposed and discussed in the TIGes
- Current criteria in force since Dec 1st 2012
- Next versions will be implemented by Sep 1st 2013

Examples of Validation Criteria

Numbe	Category	Validation Criterion	Type of check	Comments
3.4	PDF Files	Individual files in section 1.2 have no security settings except for the following, which are allowed: Changing the document Document assembly Page extraction Creation of template pages.	P/F	These limited security settings are allowable for the application form, because they are necessary for the functioning of the eAF.
3.5	PDF Files	All TOC PDF hyperlinks are relative	P/F	Absolute (rooted) links will not work once the submission has been moved to the review/assessment environment.
3,6	PDF Files	The submission does not contain corrupted files	P/F	This can be achieved by opening a PDF file in software which is compliant to ISO 32000-1; if the file opens without error, the PDF file is considered to be conformant. Absence of detection of conformance
3.BP1	PDF Files	Files have been created and saved as PDF 1.4, 1.5, 1.6, or PDF 1.7	BP	For PDF files with apparent versions of 1.3 or earlier, the version information should be taken from the first eight characters from the first line of the header in the file. For versions 1.4 and higher, the version should be taken from the document catalogue dictionary, if present. If both the header information and the catalogue information are present, then the document catalogue dictionary information takes precedent, see PDF 32000-1:2008 specification, chapter 7.5.2 for further details. Only the PDF versions specified are recommended by ICH. This test is important due to archiving and also that PDF files can be correctly open and read by assessors.
3.BP2	PDF Files	Hyperlinks and bookmarks within documents, or between documents within the same NeeS, have a valid target.	BP	Only links that open in the same software application are tested. Other links (e.g. web links and e-mail addresses) are not considered to link to essential content and should not be tested. If this BP criterion is not met, the assessor might not be able to conveniently find the relevant documents and read the submission as intended by the applicant.

Check: Pass/Fail (P/F)

- These are validation criteria that can either be passed or failed
- ALL have to be passed before start of the procedure
- May lead to delays in content validation!
  - Special note on “Y” criteria:
    Never operate on a commonly submitted document in a national submission – never operate on a nationally submitted document in a common submission

- A NeeS or eCTD sequence that fails to meet one or more of these criteria should be reported as invalid and an technically corrected submission should be submitted by the applicant – using the same sequence number

Check: Best Practice (BP)

- The applicant should always test also the BP and if not met it should be explained in the cover letter/reviewer's guide or in an added note to the submission (to prevent changing the MD5 checksum)
- eCTD or NeeS that get a "Warning" for BP criteria should still be accepted by the agency during technical validation (if no "Fail" in the P/F-test)
- Agencies should NEVER reject for BP warnings – even if the reason for them are not explained by the applicant

Restrictions in Technical Validation

- ✓ Incorrect pdf versions (only in case of version 1.3 or below)

  Missing bookmarks

  Meaningless named bookmarks

- ✓ **Broken hyperlinks within sequences or across sequences**
- ✓ **Huge pdf files, especially if unstructured**

  Scanned images and therefore no text search possible

  Badly readable paper copies badly scanned

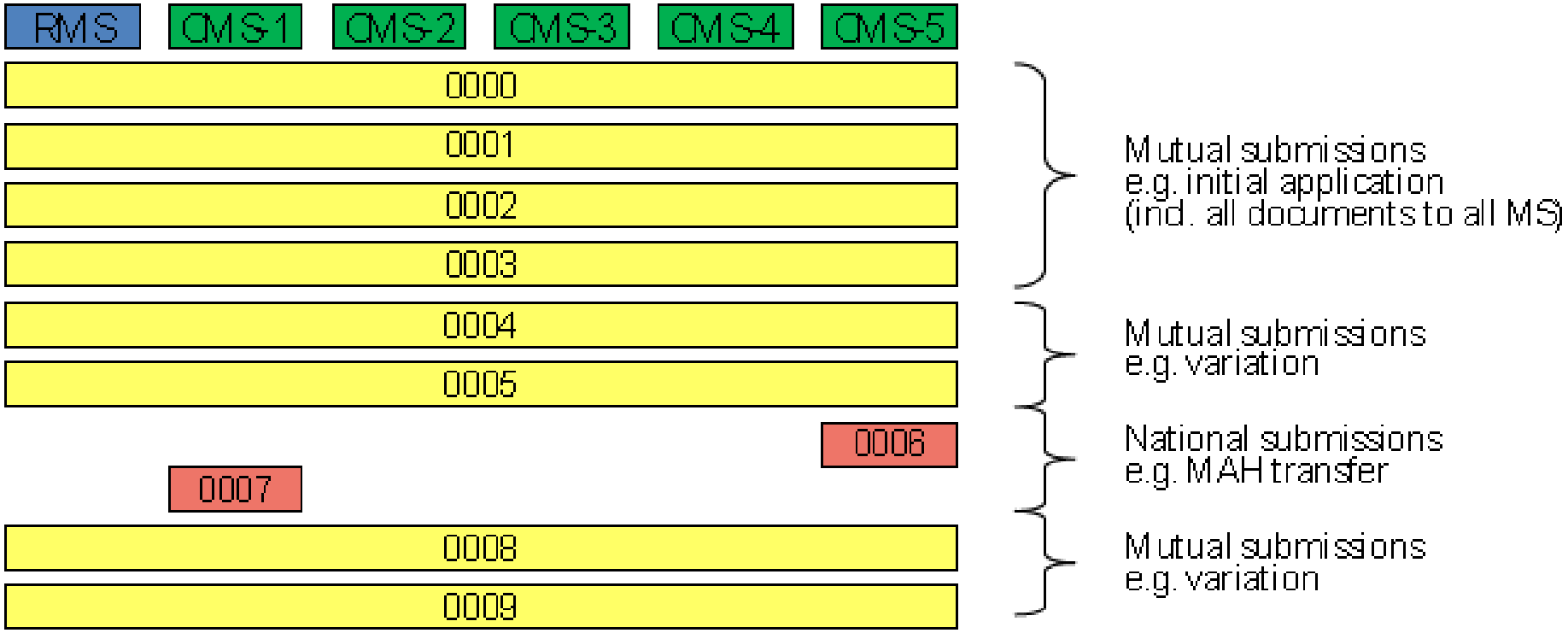
Aspects we cannot control by technical validation…

CMDh Best Practice Guide 10/2011

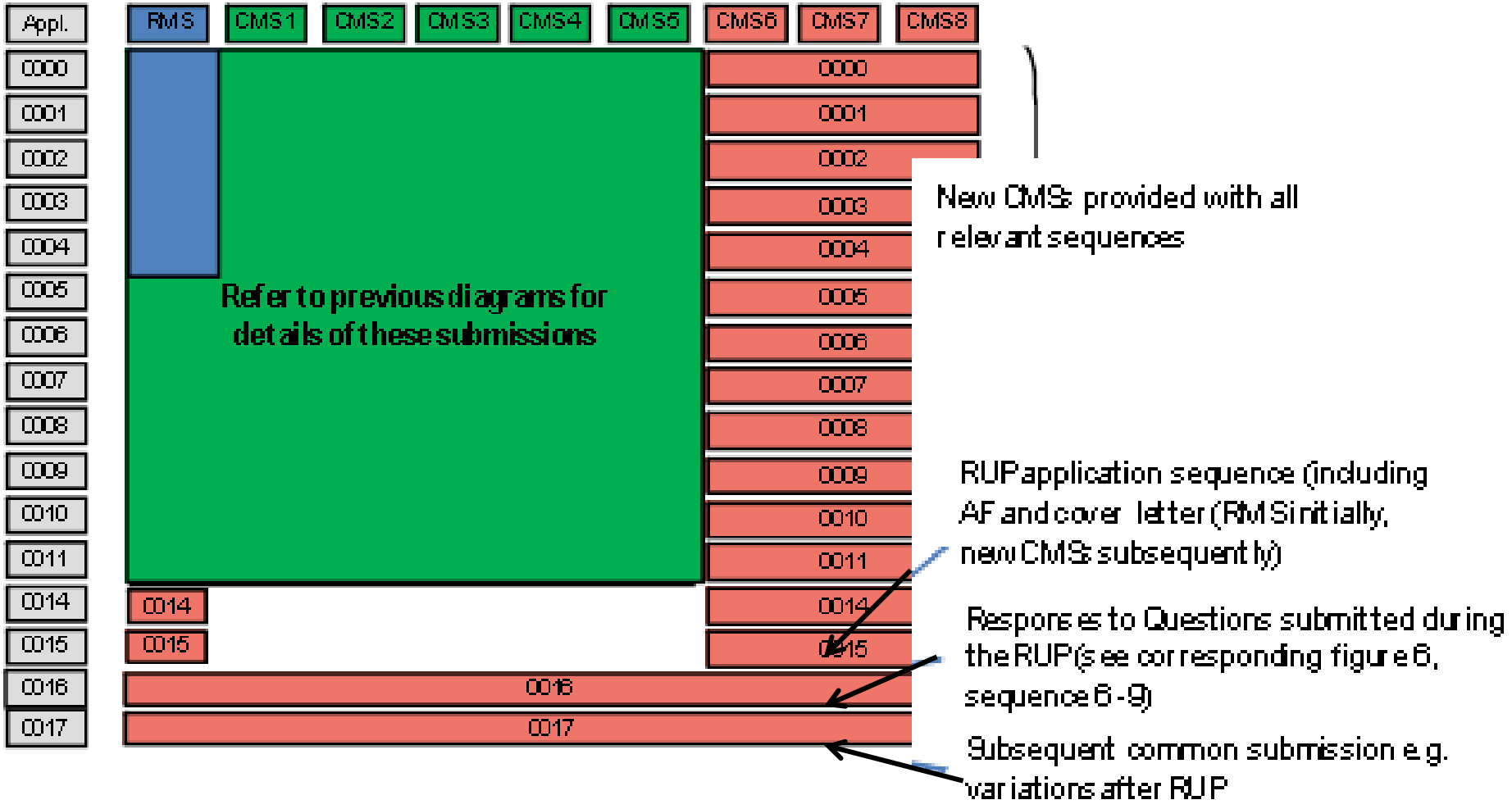
Concerning eCTD only, but for all human medicinal products

- Business rules for DCP and MRP
- Comprehensive model required, i.e. all sequences need to be distributed to all member states concerned.
- Tracking table for submitted sequences to guarantee overview on sequences distributed
- Detailing requirements on life cycle activities
- National product information text shall be excluded from eCTD dossier file

Comprehensive Model



Repeat Use Procedure (1/2)



Repeat Use Procedure (2/2)

Tracking table

Sequence	Submission description	RMS	CMSs – First Wave					CMSs – Second Wave		
		DE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SE (CMS-4)	SK (CMS-5)	FI (CMS-6)	LV (CMS-7)	NL (CMS-8)
0017	Responses to Questions	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11
0016	Manufacturing change variation	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11
0015	MRP with the new MSs has to be finalised – specific sequences for RUP-MRP – see figure 6, sequence 6-9	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11
0014	RUP initiation sequence	Dec 10	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11
0013	Responses to Questions – change in legal status (FR)				Aug 10					
0012	Change in legal status (FR)				Jul 10					
0011	Responses to Questions	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10	Jan 11	Jan 11	Jan 11
0010	Manufacturing change variation	Mar 10	Mar 10	Mar 10	Mar 10	Mar 10	Mar 10	Jan 11	Jan 11	Jan 11
0009	Day 90 – Final En product information	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Jan 11	Jan 11	Jan 11
0008	Day 85-90 Responses	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Jan 11	Jan 11	Jan 11
0007	Day 60 Consolidated Response Document	Sep 09	Sep 09	Sep 09	Sep 09	Sep 09	Sep 09	Jan 11	Jan 11	Jan 11
0006	Validation update	Mar 09	Mar 09	Mar 09	Mar 09	Mar 09	Mar 09	Jan 11	Jan 11	Jan 11
0005	Country specific information (All)	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0004	MRP update sequence	Jan 09	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0003	Final agreed National product information	Dec 08	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0002	Responses to questions	Sep 08	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0001	Validation update	Dec 07	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0000	Initial MAA	Dec 07	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11

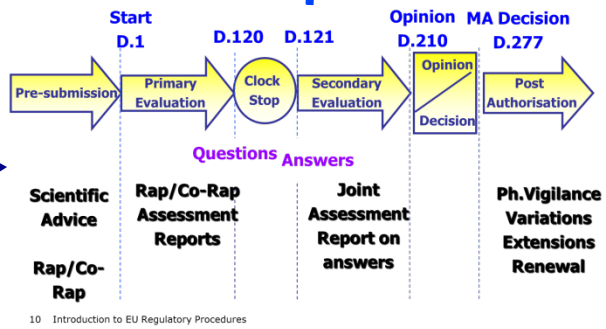
Agencies' Expectations

- Receipt of instantly growing number of e-only submissions
- Strategies for promoting industry willingness to switch
- Agreement about target date to request mandatory e-only submission
- Improvement of dossier quality to achieve advantages of electronic submissions

From submission to publication:

CAP Example

Electronic submission



Centralised Procedure (e.g.)

AR

CHMP Opinion

(incl Annex A and I-IV)

...

Medicines Under Eval

SMOP or Refusal Q&A

EPAR

CxMP Meeting Docs

Future Proactively Published Info

EC Decision

...

Information via AtD

Info submitted | Validation and assessment | Info published