„Vom CTD zum eCTD“
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Switching from Paper to eCTD: Real life examples

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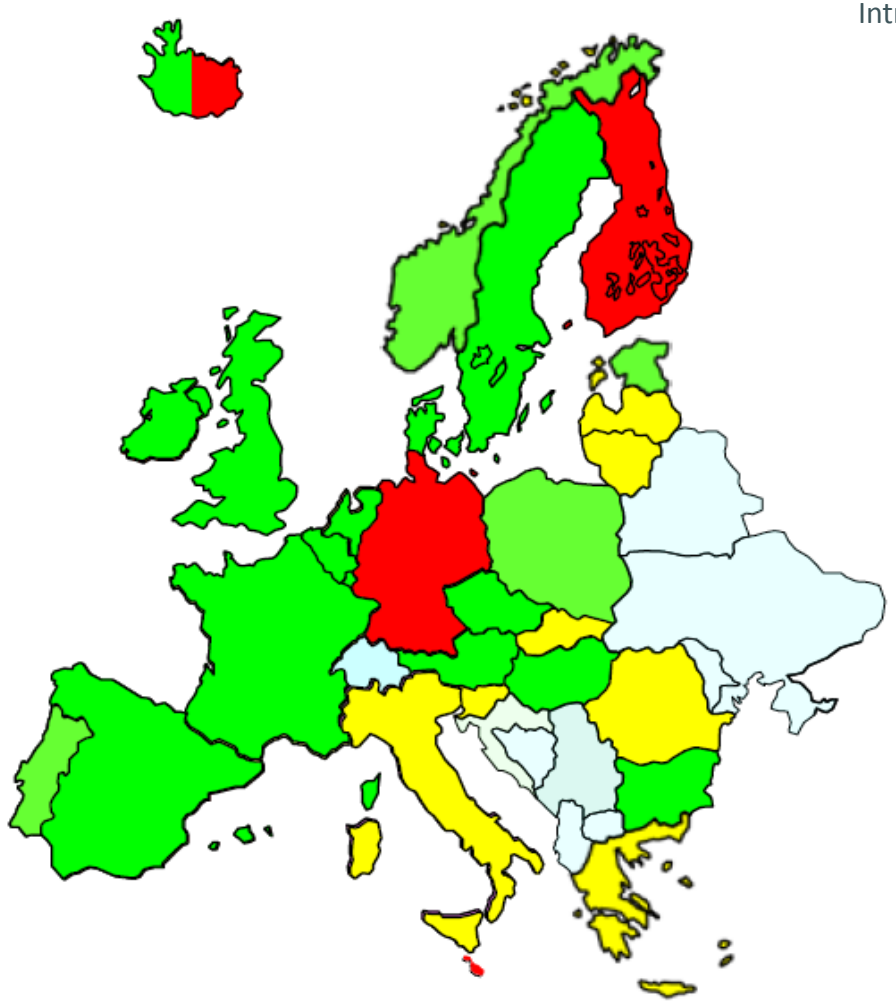
Topics

- Short Introduction
  - eCTD
  - Baseline
- Real-life examples for switching to eCTD
  (1) in the pre-authorization phase
  (2) in the post-authorization phase *using eCTD baseline*
  (3) in the post-authorization phase *without eCTD baseline*
- Conclusion

Status eCTD
EU implementation

- eCTD
  - Mandatory electronic-only standard for EU CP, US, CA, CH
  - Recommended standard for EU MRP/DCP
    - NeeS interim standard
- Implementation status EU
  - 2010: EMA mandates eCTD as only eSubmission standard
    EU NCAs to accept eCTD as electronic-only standard
  - Majority of NCAs met deadline, few are remaining
  - Still some heterogeneous paper requirements for signed documents (cover letter, application form, ...)

Status eCTD
EU implementation



Source:
HMA special press release
Nov 2009

Map by Läkemedelsverket
Medical Products Agency
Sweden

When to start with eCTD?

- Start with eCTD “from the beginning” i.e. with initial application
- Switch to eCTD (from NtA, CTD, NeeS)
  - Running procedure(s) should be completed first
  - After initial Marketing Authorization has been granted, before starting post-authorization activities
  - Any time during post-approval lifecycle, except for running regulatory activities (e.g. type II variation)

eCTD Baseline

What is an eCTD baseline?

- Purely “formal” eCTD lifecycle initiation step
  - No new contents to be included
  - Not subject to review, only uploaded into review system(s)
  - Submission type “reformat”
  - Hyperlinks not required
  - Ideally in timely context of a new regulatory activity
- Should at least include
  - M3 Quality documents that reflect the current regulatory approved status
  - Current product information files (“common” for MRP/DCP)

Real-Life Example 1

Shifting to eCTD during the pre-authorization phase of a large EU DCP

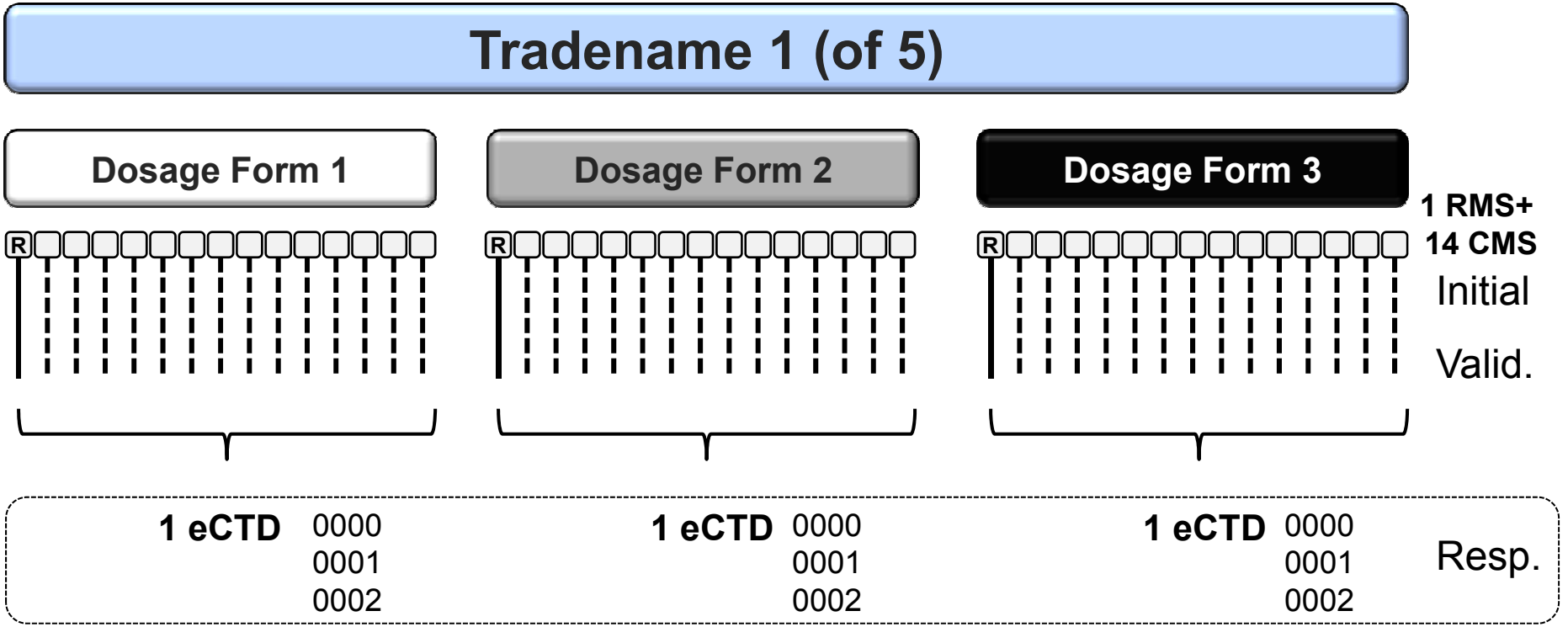
Example 1
Objectives

- Example 1: Pre-authorization phase
  - EU DCP in 15 countries
  - Generic applications: Multiple tradenames, strengths and dosage forms with individual dossiers
  - To switch from paper and “eCTD-like” dossier to true eCTD
  - To switch from “parallel national” to comprehensive eCTD

Example 1
Starting point

- „Master Dossier“ present in „eCTD-like“ format for RMS:
  - 0000 initial submission (209 documents)
  - 0001 response to validation (59 documents)
- CMS submissions performed locally in paper and/or “NeeS-like”
- CMS M1 specific documents present locally, core documents available centrally
- To be switched to eCTD for „response to PAR“ in sequence 0002

Example 1
Overview



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Example 1
Challenges

- In total 5 tradenames, each with 3 dosage forms
  ⇨ 15 dossiers to be prepared in parallel
- Submitted sequences 0000 + 0001 were rebuild and supplemented with CMS related M1 documents
- M1 documents (cover letters, application forms,….) prepared locally, eCTD compilation & publishing centralized
- 0002 consisted of 261 documents (mainly M4 + M5 literature)!
- Very tough deadlines!
- Accomplished in ~ 14 working days (using 3 FTEs)

Example 1
Benefits realized

- From 3 x 5 x 15 = 225 individual dossiers ⇨ 15 dossiers
  - Greatly reduced overall complexity
  - Workload and know-how has been centralized
  - “Current” dossier content became much more transparent
  - Submission status much easier to track
  - Significant cost reduction for follow-up lifecycle

Real-Life Example 2

Shifting to eCTD in the post-authorization phase using a baseline submission

Example 2
Objectives

- Example 2: Post-authorization phase
  - EU DCP in 3 countries
    - Generic applications: Multiple tradenames, strengths and dosage forms with individual dossiers (9 in total)
  - To switch from paper to eCTD using eCTD baseline submission
    - Built from approved application and 1 subsequent type IB variation
  - Several variations to be filed subsequently “in parallel”

Example 2
Starting point

- Documentation was available in electronic format
- M3 documents partly to be reformatted
  - Granularity
  - PDF settings, bookmarks etc
- Different variations for individual dosage forms to be compiled directly after baseline

Example 2
Overview

Tradename 1 (of 3)

Dosage Form 1	Dosage Form 2	Dosage Form 3	
Initial Procedure	Initial Procedure	Initial Procedure	Paper / NeeS
Type IB	Type IB	Type IB	Paper / NeeS
Baseline	Baseline	Baseline	0000
Type IA	Type IA	Type IA	0001
Type IA	Type IA	Type II	0002
Type IA	Type IA	Type II	0003
Type IA	Type IA	Type IA	0004
Type II	Type IB		0005
Type IB			0006
Type IB			0007

eCTD LCM

Example 2
Baseline

- M3 consisted of ~ 1000 - 1150 pages
- 1 x section 3.2.S, 1 x section 3.2.P, 1 x section 3.2.P.4
- “General” data chosen for eCTD attribute “manufacturer” in 3.2.S and 3.2.P
- High level of granularity chosen for M3
- In total 91 - 104 M3 documents
- Additionally M2 and M4-M5 documents included, as well as core M1 documents (not mandatory for baseline)

Example 2
Baseline (cont'd)

- Low level of hyperlinking in M3 due to expected frequent lifecycle updates
- Comprehensive TOCs and "Module TOCs" from CTD / NeeS not included in eCTD
- "Divider pages" from CTD (e.g. "not applicable") not included in eCTD

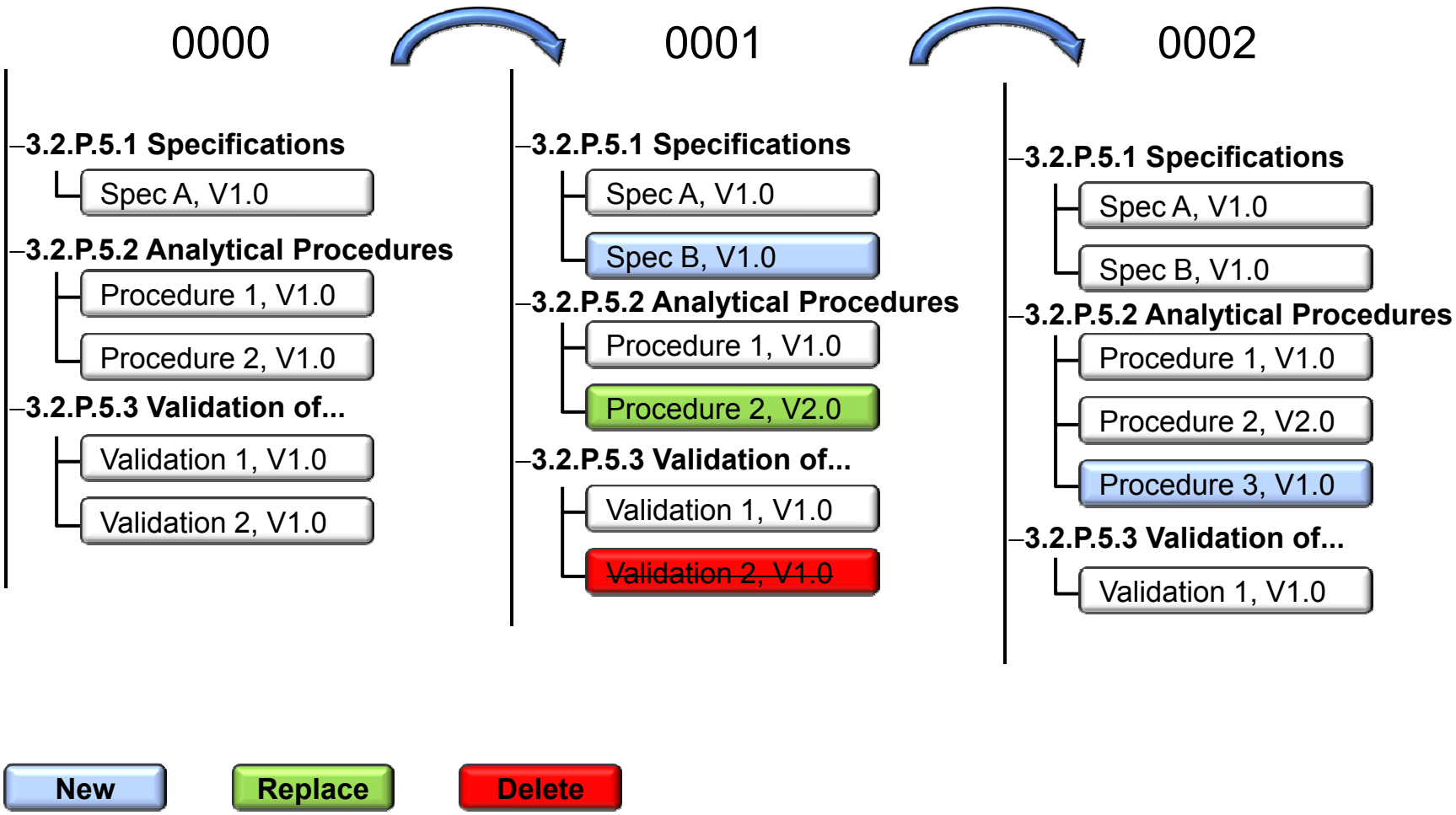
Example 2
Challenges baseline

- Granularity to be defined based on expected future lifecycle
  - Change from how documents were written in the past
  - „Section documents“ split in individual files for higher granularity
- How to rework “section overview” documents in M3?
- Where to place additional explanatory documents not allocated to a specific eCTD section?
- How to deal with older documentation (paper, scanned images)?
- Ensuring proper PDF format and settings for existing electronic documentation

Example 2
Challenges parallel variations

- Several variation sequences to be compiled in close timely context, to be submitted “in parallel”
  - Document availability did not always reflect the order of sequence preparation
  - Need for change of early sequence(s) at late stage of preparation when later sequences have already been compiled

Compiling multiple sequences



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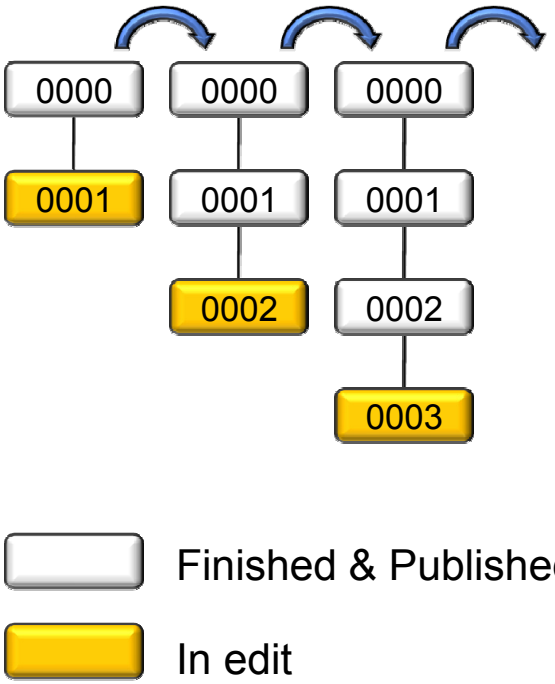
Compiling multiple sequences



- eCTD *sequences* are usually built "*sequential*"
- Information for eCTD leafs is inherited
- Seq 0001 should be finalized & published before building 0002, etc...
- Compiling multiple sequences "at once":
  - Close coordination required between authors and eCTD publisher
  - Documents should be available in order of their corresponding sequence
  - Cave: Late changes in already published sequences!

Example 2
Challenges eCTD lifecycle

- Document granularity to be consistent throughout eCTD lifecycle updates
- eCTD lifecycle attributes limited to „new“, „replace“, „append“, or „delete“ (ICH eCTD spec. 3.2.2)
- Documents already submitted should not be submitted again in later sequences unless they have been subject to changes

Change in philosophy: Stand-alone “variation packages” vs consistent electronic lifecycle

Example 2
Challenges eCTD lifecycle

- Change in philosophy: from stand-alone “variation packages” to consistent electronic lifecycle

	“Classical Packages”			True eCTD LCM		
Variation Type	IA	II	II	IA	II	II
Sequence / Docs	0001	0002	0003	0001	0002	0003
Annex 5.22	resub.	resub.	resub.	?	?	?
1.4.1 Quality		resub.	resub.		?	?
2.3.P		resub.	resub.		?	?
3.2.P.3.1	updated	resub.		replace	?	
3.2.P.3.2		updated	resub.		replace	?
3.2.P.3.5		updated	resub.		replace	?

Example 2
Challenges eCTD lifecycle

- Submitted in 2009, additional paper was still requested at that time
- Feedback from RMS: “We need all documents relevant for the variations, independent whether they have been submitted already previously”

→ Accompanying paper submission contained complete set of documents, eCTD was built according to specification

→ Annex to cover letter included in eCTD with hyperlink references to relevant documents in previous sequences

Example 2
Changing philosophy

- The eCTD does not know operation attributes like “resubmit” or “included again”...

	“Classical Packages”			True eCTD LCM		
Variation Type	IA	II	II	IA	II	II
Sequence / Docs	0001	0002	0003	0001	0002	0003
Annex 5.22	resub.	resub.	resub.	referenced	referenced	referenced
1.4.1 Quality		resub.	resub.		referenced	referenced
2.3.P		resub.	resub.		referenced	referenced
3.2.P.3.1	updated	resub.		replace	referenced	
3.2.P.3.2		updated	resub.		replace	referenced
3.2.P.3.5		updated	resub.		replace	referenced

Real-Life Example 3

Shifting to eCTD in the post-authorization phase without using a baseline submission

Example 3

- Example 3: Post-authorization phase
  - National licensed product (Spain)
  - 1 tradename, 1 strength and dosage form
  - To switch from paper dossier to eCTD *without prior submission of a baseline eCTD*

Example 3
Starting point

- No baseline submission due to timely constraints and low resources
- M3 documents reformatted in CTD format as required per lifecycle sequence concerned
- eCTD lifecycle to start with a type II variation, several sequences filed “in parallel”
- Trigger: Subsequent renewal procedure

Example 3
Preconditions

- Quotation from AEMPS website

*"...**IMPORTANT:** The switch from paper to electronic-only can be made **at the start of any phase in the life cycle of a medicinal product, initial application or a later variation**. Once the switch to electronic-only is made it is highly recommended that further applications and responses relating to the particular medicinal product are submitted in electronic format. **Historical data does not need to be re-submitted electronically**... "*

Example 3 Overview

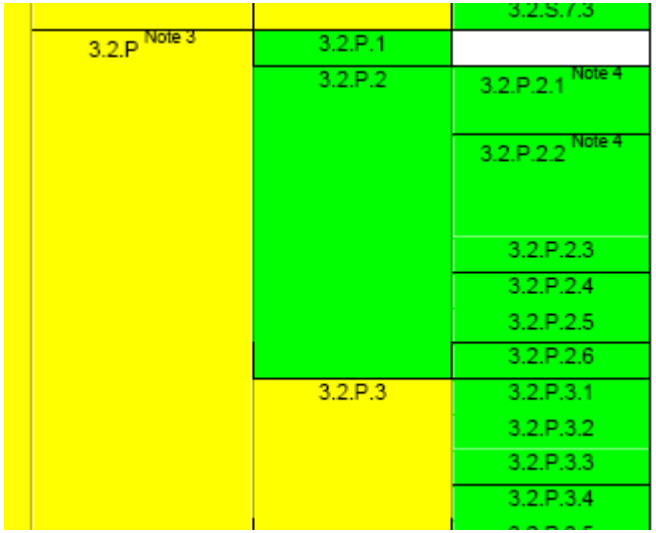
Tradename 1

Dosage Form 1

Distinct Points in time	Paper Dossier (NtA, CTD, ...)		
1	Type II	0000	"in parallel"
	Type IA	0001	
	Renewal	0002	
2	Supplement	0003	
3	Type IA	0004	"in parallel"
	Type IB	0005	
	Type II	0006	
	Type II	0007	

Example 3
Granularity guidance

- ICH eCTD specification 3.2.2: „*Refer to the Granularity Annex of the M4 Organisation Document for guidance on the flexibility of multiple documents for Module 3*"



Taken from the "Guidance for Industry: Granularity Document
Annex to M4: Organization of the CTD"

- Some examples for high level granularity (multiple file approach) given in ICH spec (e.g. 3.2.S.4.2; 3.2.S.4.3)

Some level of flexibility in the eCTD with regards to Granularity of M3

Example 3
Basic challenges

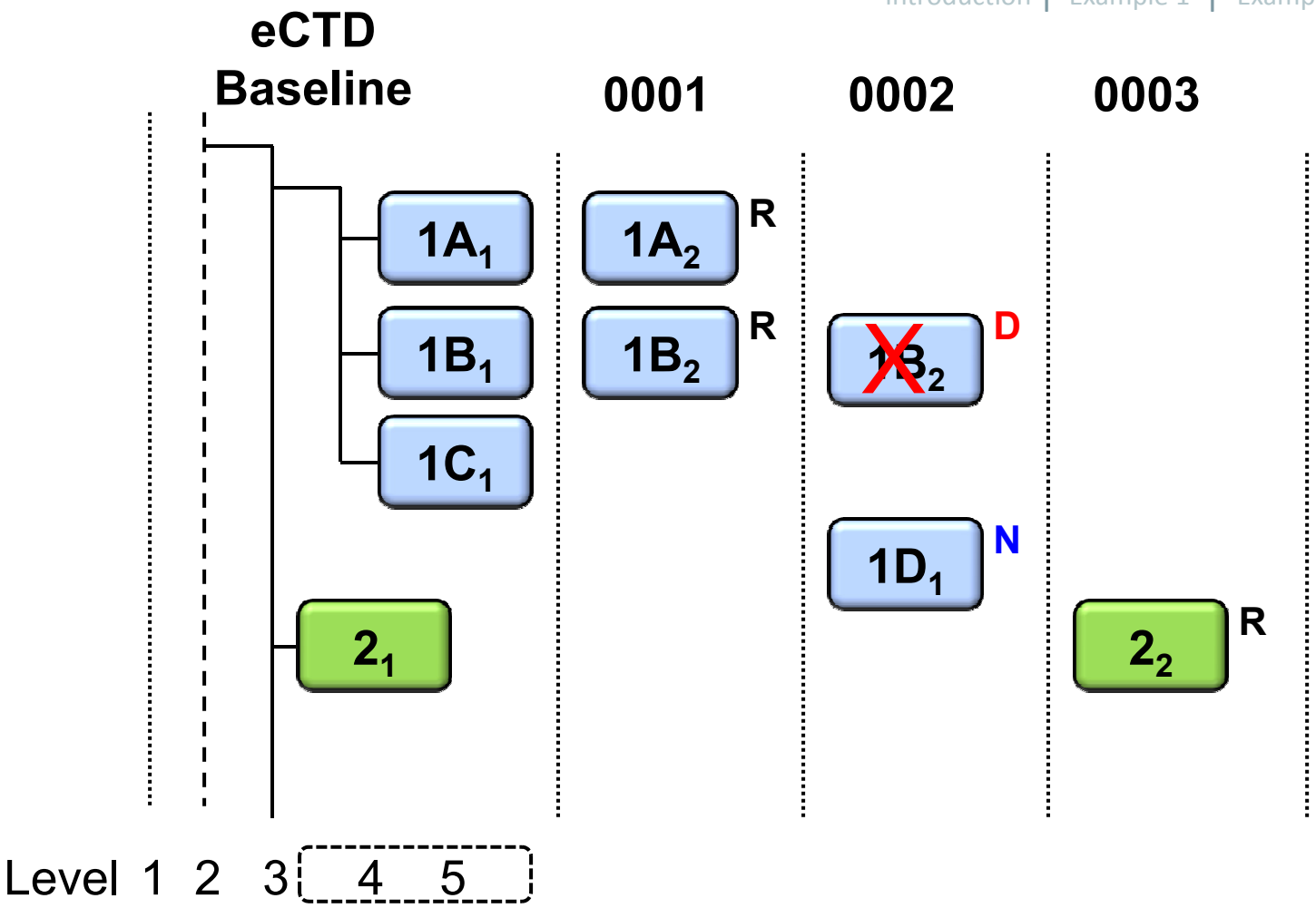
- Basically the same challenges as for example 2
  - How to rework “section overview” documents in M3?
  - Where to place additional explanatory documents not allocated to a specific eCTD section?
  - How to deal with older documentation (paper, scanned images)?
  - “Parallel” compilation of multiple sequences

Not to compile a baseline does not mean you don’t have to think about building a proper eCTD

Example 3
Special challenges

- No “baseline” (hence the name!) against to check
  - Difficulties in establishing the right level of granularity throughout the eCTD lifecycle
  - High risk of running into problems with assigning correct “operation” attributes (new, replace, delete, append) for eCTD lifecycle
- Dossier assembled sequence per sequence
  - No “current view” of the complete dossier (historical documents not yet included in eCTD need to be accounted)
  - Higher risk of inconsistent content

Predefined Granularity level



R = Replace
N = New
D = Delete

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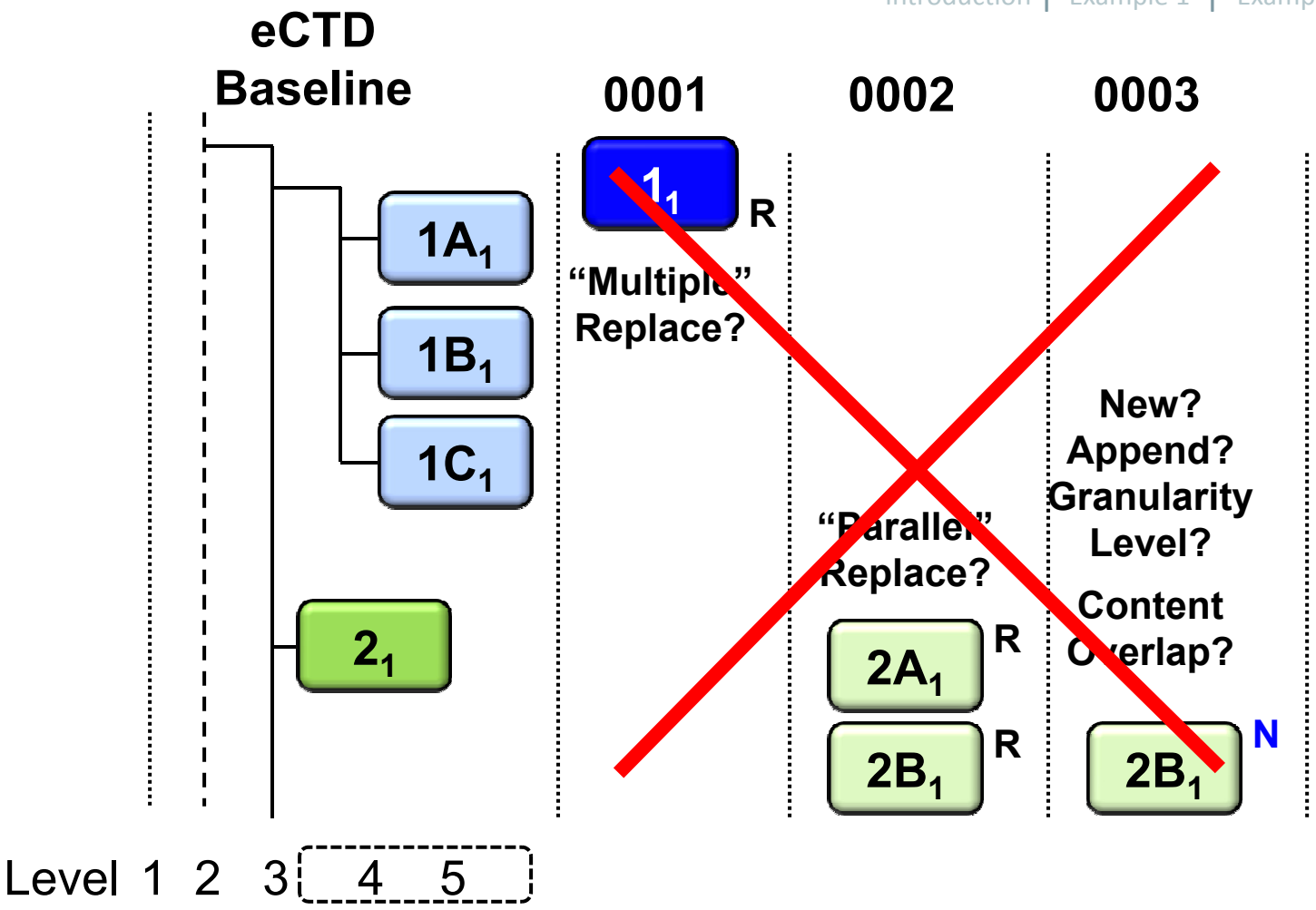
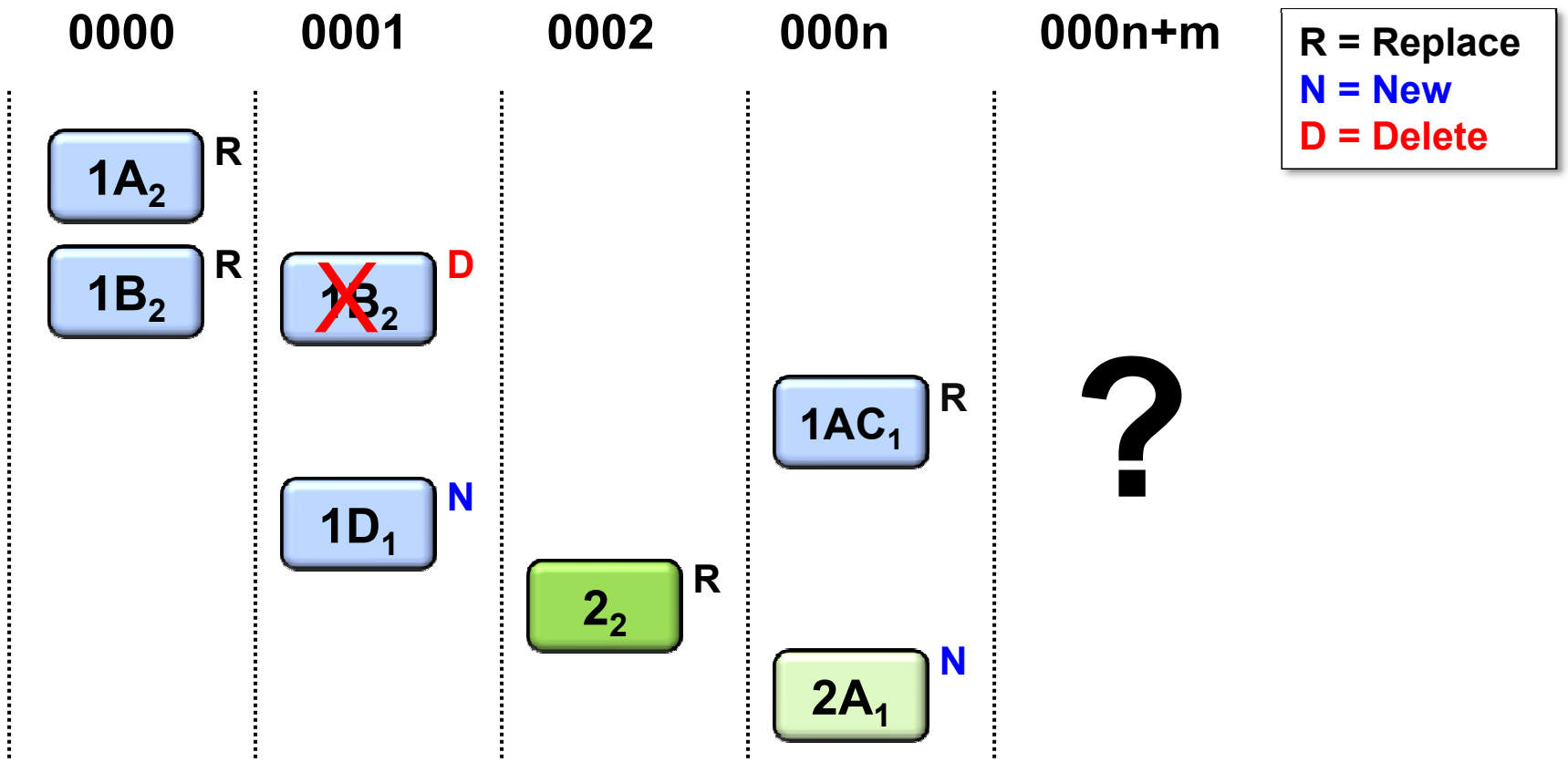
Predefined Granularity level



No predefined Granularity level



"Fun" through Granularity issues

0000

3.2.S.2.3 **Doc. 1**
1) Material A
2) Material B
3) Material C

3.2.S.2.3 **Doc. 2**
4) Material D
5) Material E

000n

3.2.S.2.3 **Doc. 3**
6) Material F
7) Material G

New ?

Current

3.2.S.2.3 **Doc. 1**
1) Material A
2) Material B
3) Material C

3.2.S.2.3 **Doc. 2**
4) Material D
5) Material E

3.2.S.2.3 **Doc. 3**
6) Material F
7) Material G

"Fun" through Granularity issues

0000

3.2.S.2.3 **Doc. 1**
1) Material A
2) Material B
3) Material C

3.2.S.2.3 **Doc. 2**
4) Material D
5) Material E

000n

3.2.S.2.3 **Doc. 3**
1) Material A, V2
2) Material B, V2
6) Material H

New ?

Current

3.2.S.2.3 **Doc. 1**
1) Material A
2) Material B
3) Material C

3.2.S.2.3 **Doc. 2**
4) Material D
5) Material E

3.2.S.2.3 **Doc. 3**
1) Material A, V2
2) Material B, V2
6) Material H

“Fun” through Granularity issues

0000

3.2.S.2.3 **Doc. 1**
1) Material A
2) Material B
3) Material C

3.2.S.2.3 **Doc. 2**
4) Material D
5) Material E

000n

3.2.S.2.3 **Doc. 3**
1) Material A, V2
2) Material B, V2
6) Material H

Replace ?

Current

3.2.S.2.3 **Doc. 3**
1) Material A, V2
2) Material B, V2
6) Material H

3.2.S.2.3 **Doc. 2**
4) Material D
5) Material E

~~3) Material C~~

Conclusion

Lessons to learn from the examples

Approach during procedure

- Needs to be agreed with your agencies
- Usually requires proper rebuilding of the already performed pre-approval lifecycle
- Spares a baseline submission afterwards
- Puts you under time pressure due to the fixed milestones of the corresponding MAA procedure

Start with initial submission or
wait until completion of the procedure!

Approach with baseline

- Select granularity carefully and consider expected frequency of changes for each M3 section
- Continue granularity levels as established with baseline
- Remember: Granularity is defined by the content - avoid combining mixed content for granular documents and sections
- Select appropriate data for eCTD attributes „substance“, „manufacturer“, „product“, „dosage form“, „excipent“
- PDFs rendered from source files are preferred, try applying descriptive header / footer per each granular document
- Use short but meaningful leaf titles

Approach without baseline

- Same considerations as for the baseline approach still apply!
- In case of doubts, the highest possible level of granularity at the start of the eCTD lifecycle should be preferred
- Assure that the next sequence(s) matches the granularity level of the previous sequence(s)
- „Current view“ of dossier does not exist, tracking of dossier content and regulatory status of individual documents is more difficult
- Only short-term advantage, more disadvantages in the long-term
- Not recommended for complex procedures

General

- Switching from paper to eCTD
  - is a change in the philosophy of how documents and dossiers are prepared
  - has larger impact on document writing and archiving processes
- The eCTD and its lifecycle concept still needs to be embraced more by regulatory agencies and applicants alike!

Thank You

"Make everything as simple as possible, but not simpler"

Albert Einstein

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