DIA 2019
Eurasia
Moscow | October 23

# Case Studies on eCTD

## Review and validation and on eCTD Lifecycle Management

Hans van Bruggen, MSc
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www.Qdossier.com

Qdossier.

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# Disclaimer – Use of demo tool

- Use cases in these slides are illustrated by using a viewing tool
- There are more viewing tools available by various vendors
  - Examples: Lorenz, eXtedo, Synchrogenix
- We are most familiar with this tool and we can access it freely, hence we use this tool.

# Agenda

- Who are we?
- Introduction to lifecycle management
- Circular information management
- Separate content from context
- How does the EAEU eCTD fit in this?
- Regulatory affairs and circular information management
- eCTD lifecycle in practice
- Use cases
- Concluding remarks

# Who are we?

Marloes van der Geer

Hans van Bruggen

Show of hands: Who are you?

# Marloes van der Geer

- Regulatory Affairs Scientist at Qdossier
  - Consultancy, services and solutions
- ~10 years in Pharmaceutical Industry
  - 2010 F.Hoffmann – la Roche Traineeship Regulatory Affairs
  - 2012 F.Hoffmann – la Roche Regulatory Intelligence EU and MoW
  - 2015 F.Hoffmann – la Roche Regulatory Policy EMEA region
  - 2019 – Qdossier Regulatory Affairs Scientist

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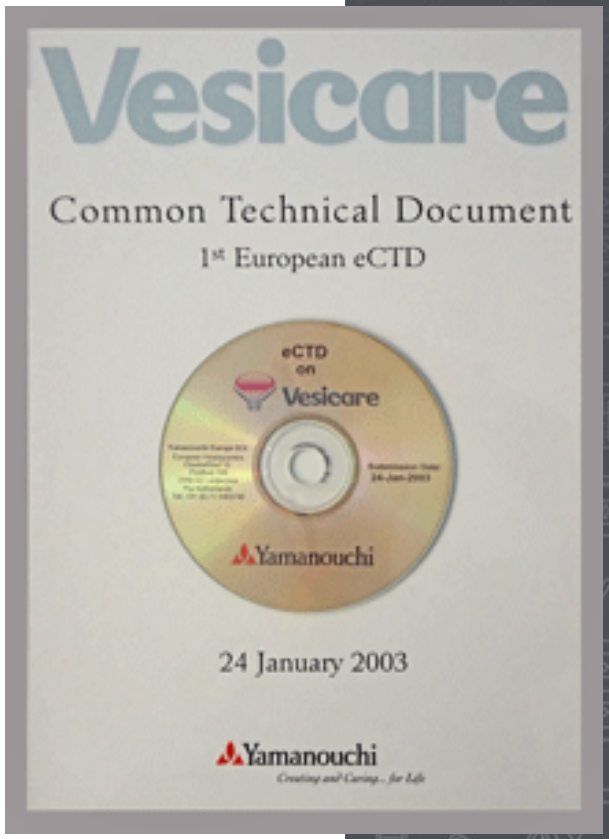
# Hans van Bruggen

- CEO & Founder Qdossier
  - Consultancy, services and solutions
- >35 years in Pharmaceutical Industry
  - 1981 Organon Toxicology
  - 1992 Organon Regulatory Affairs
  - 2001 Yamanouchi Regulatory Affairs
    - Build and submitted the first eCTD for a NCE Worldwide
  - 2003 J&J Regulatory Operations
    - Set up a global Reg Ops department to support eSubmissions
  - 2006 Established Qdossier
    - Headcount: 20+

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# Show of hands: Who are you?

- Industry
- Agencies
- Software vendors
- Consultants and service providers
- Regulatory Affairs, focusing on content and context
- Regulatory Operations, focusing on operations
- IT
- Less than 5 years in Life Science
- Less than 5 years in Regulatory

# Introduction to lifecycle management

Product lifecycle (e.g. Initial MAA followed by variations)

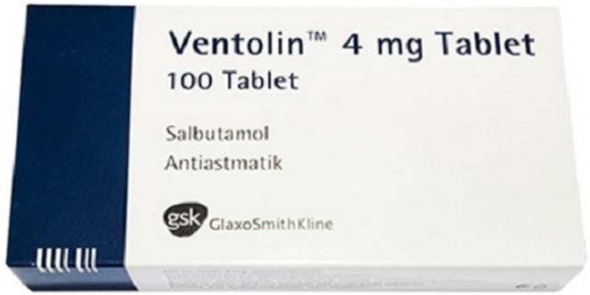
Dossier and document lifecycle

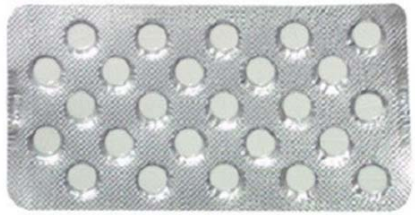
Data lifecycle

# Product lifecycle

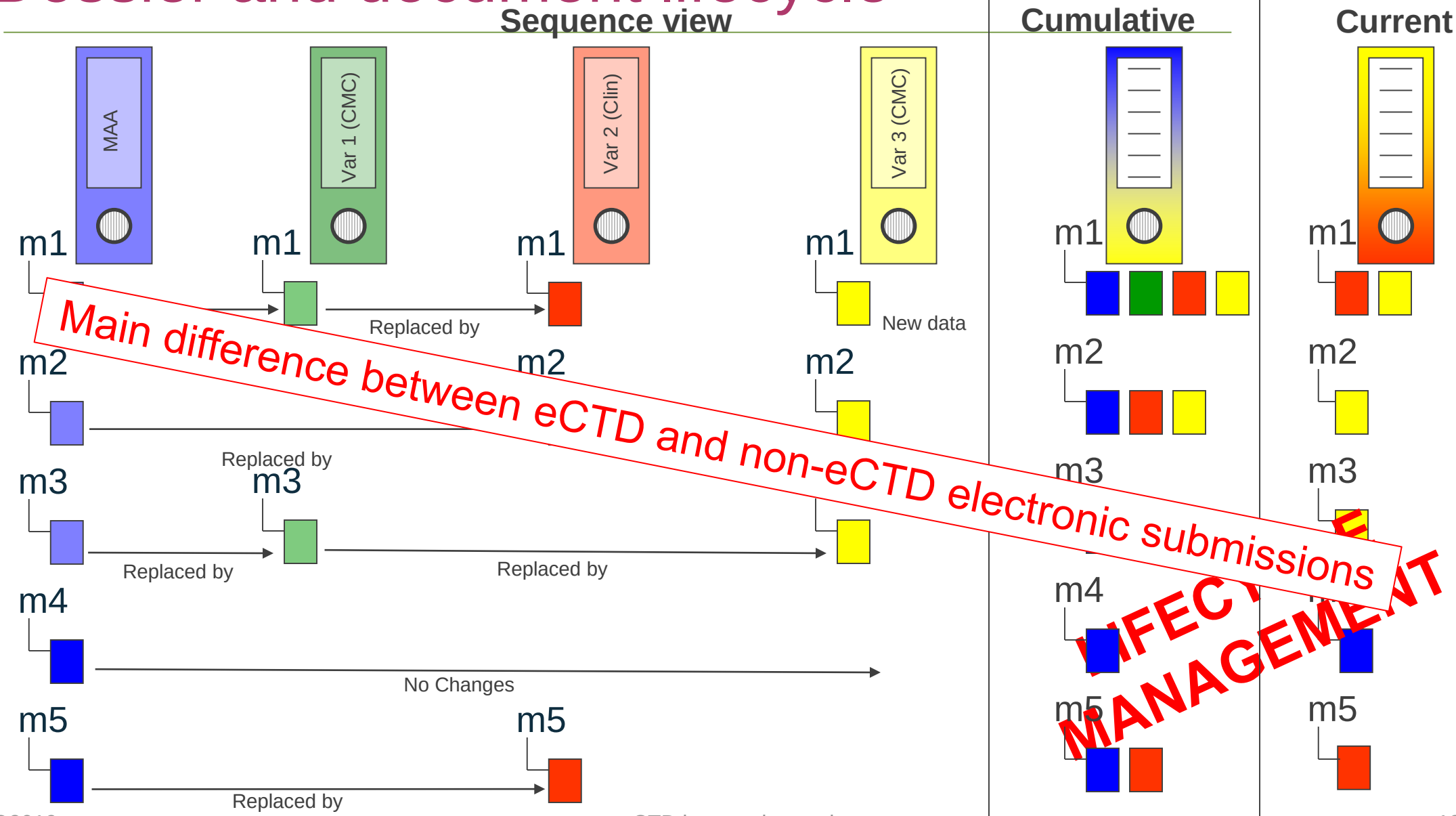
- Initially often one formulation and strength
  - In one or multiple countries
  - With or without agents or local marketing partners
- Later more formulations and multiple strengths
- Later multiple changes to introduce additional or other ……
  - Indications and contraindications
  - Adverse events, warnings and precautions
  - Manufacturers
  - Suppliers of raw materials and packaging
  - Additonal stability data
  - Periodic benefit/risk evaluation reports
  - Etc.

# Product lifecycle example




# Dossier and document lifecycle

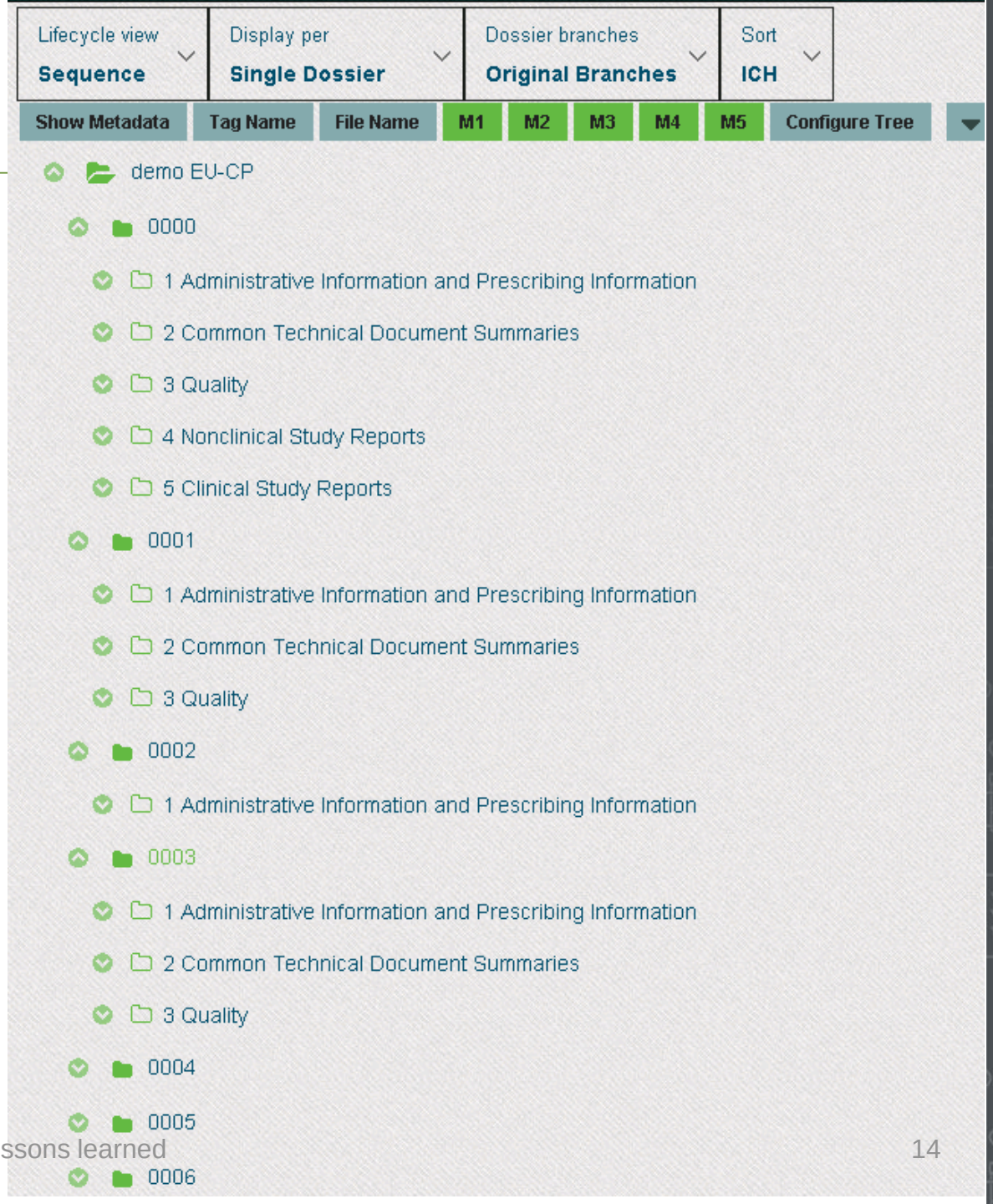


# Advantages of eCTD lifecycle – an illustration

- Was a particular adverse event labeled or unlabeled in the product information at the time the AE was reported?
- In which countries have I used the Manufacturer ‘Waalwijk’ where I have findings with my audit?
- For which products do I have to update the quality standard about Excipient ‘Magnesium stearate’?
- What is the current status of the specifications of ‘ProduQt’ in ‘EU MRP’?
- What stability duration has been submitted where?

# Sequence view

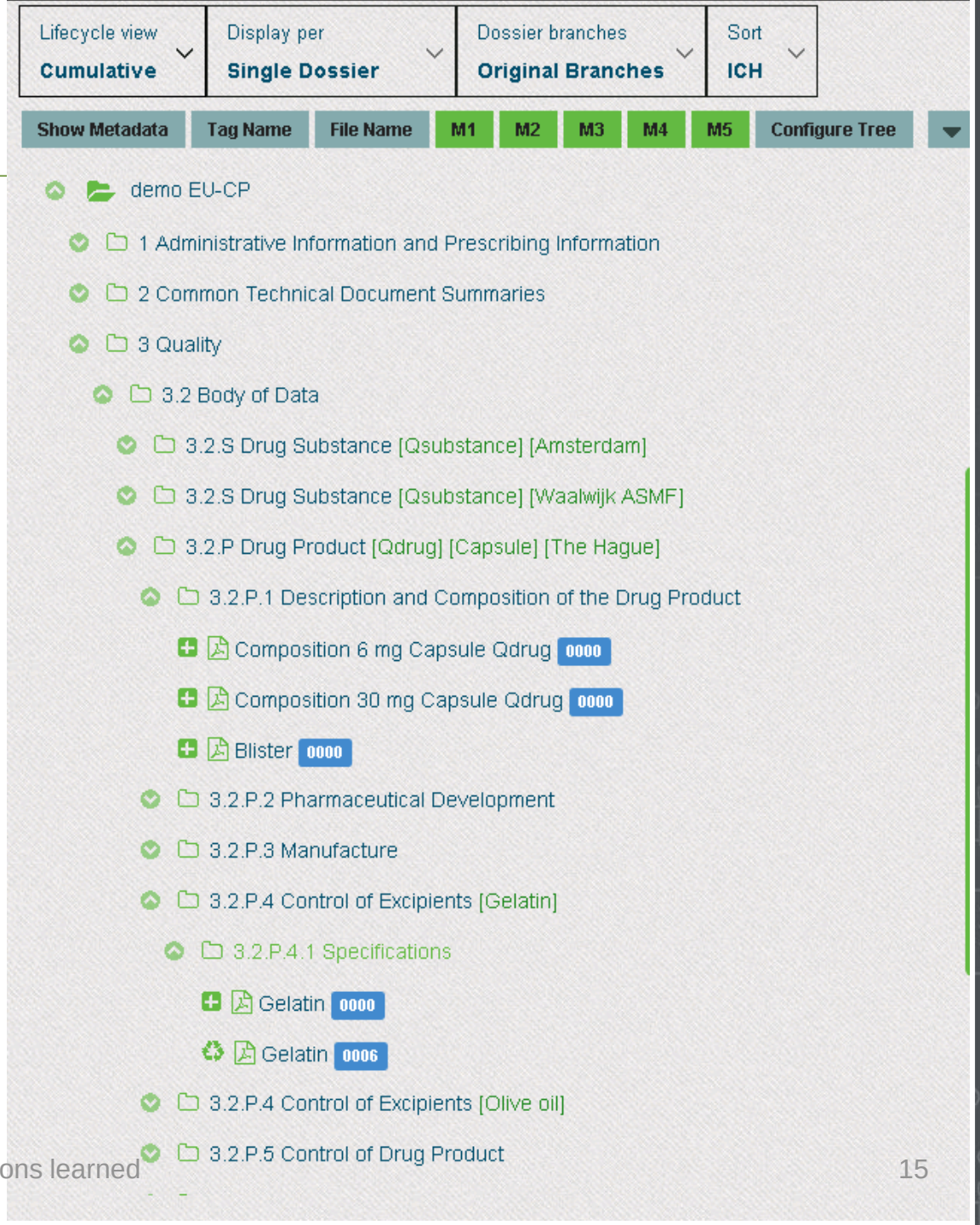
- Each sequence is shown separately
- Documents sorted per sequence
- Possible for eCTD and NeeS



# Cumulative view

- All sequences submitted shown
- All versions of the document submitted shown

- Possible for eCTD and NeeS

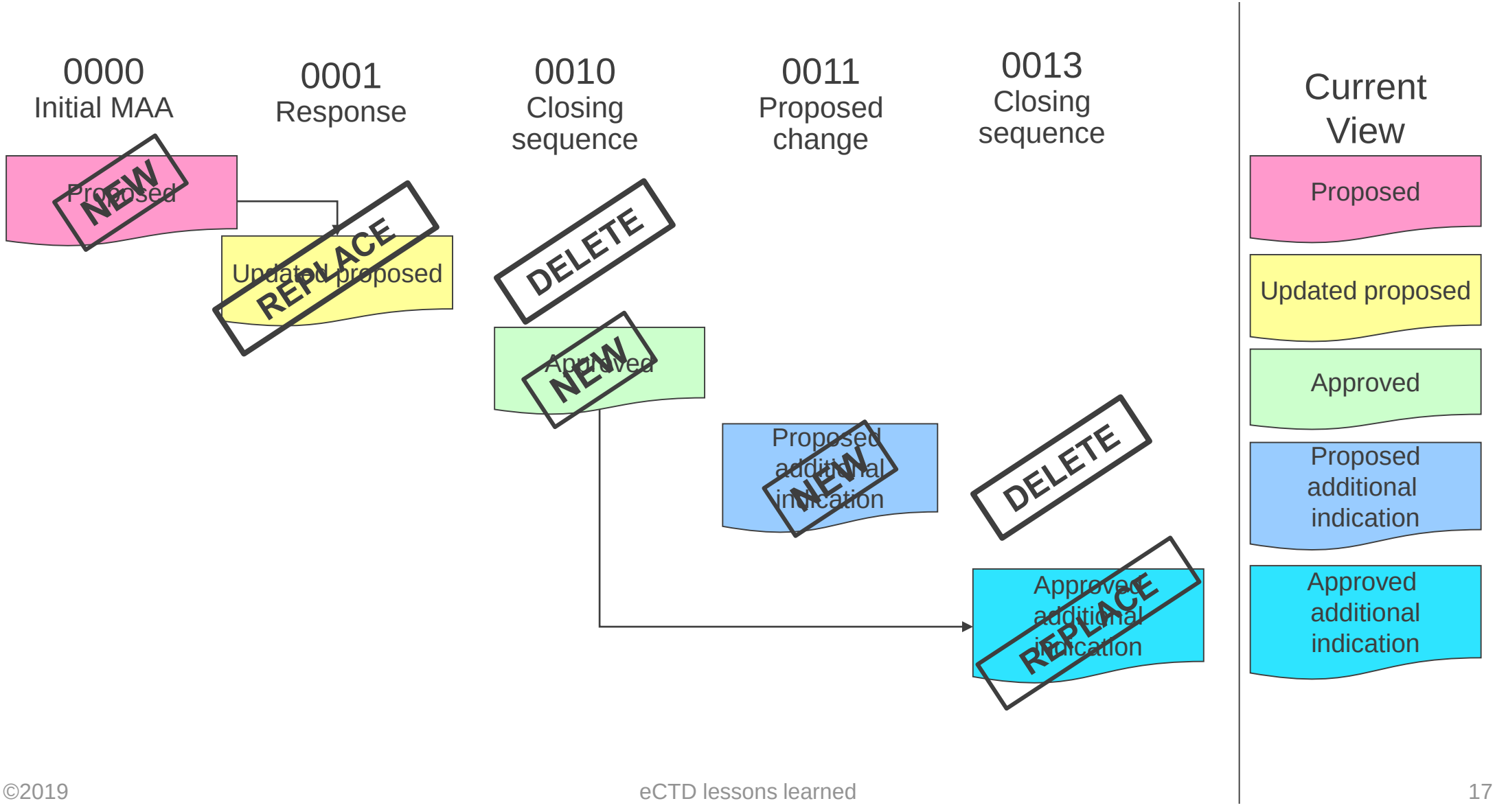


# Current view

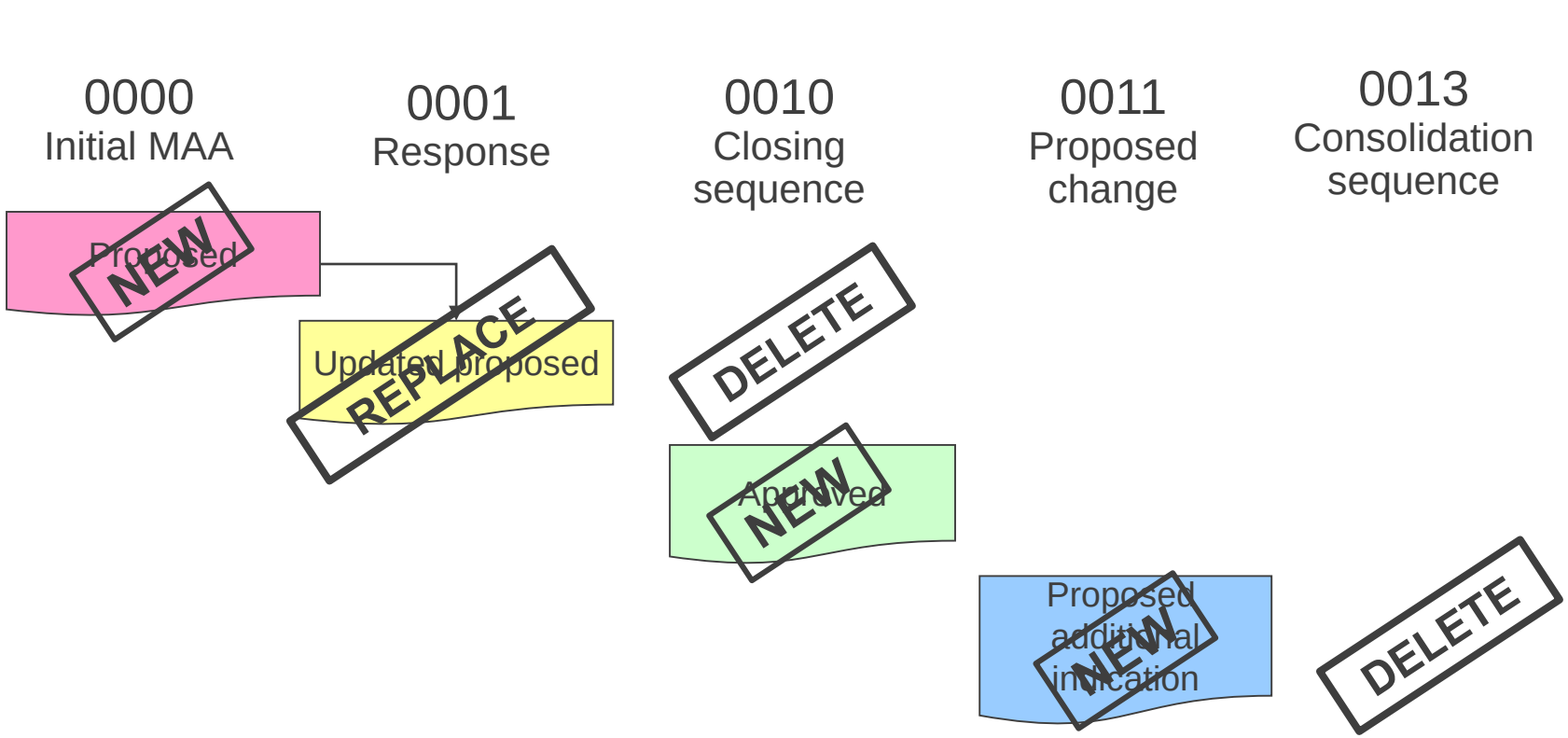
- Current status of the dossier is shown
- Latest version of the document submitted shown only

- Only possible for eCTD

# Document lifecycle example for product information



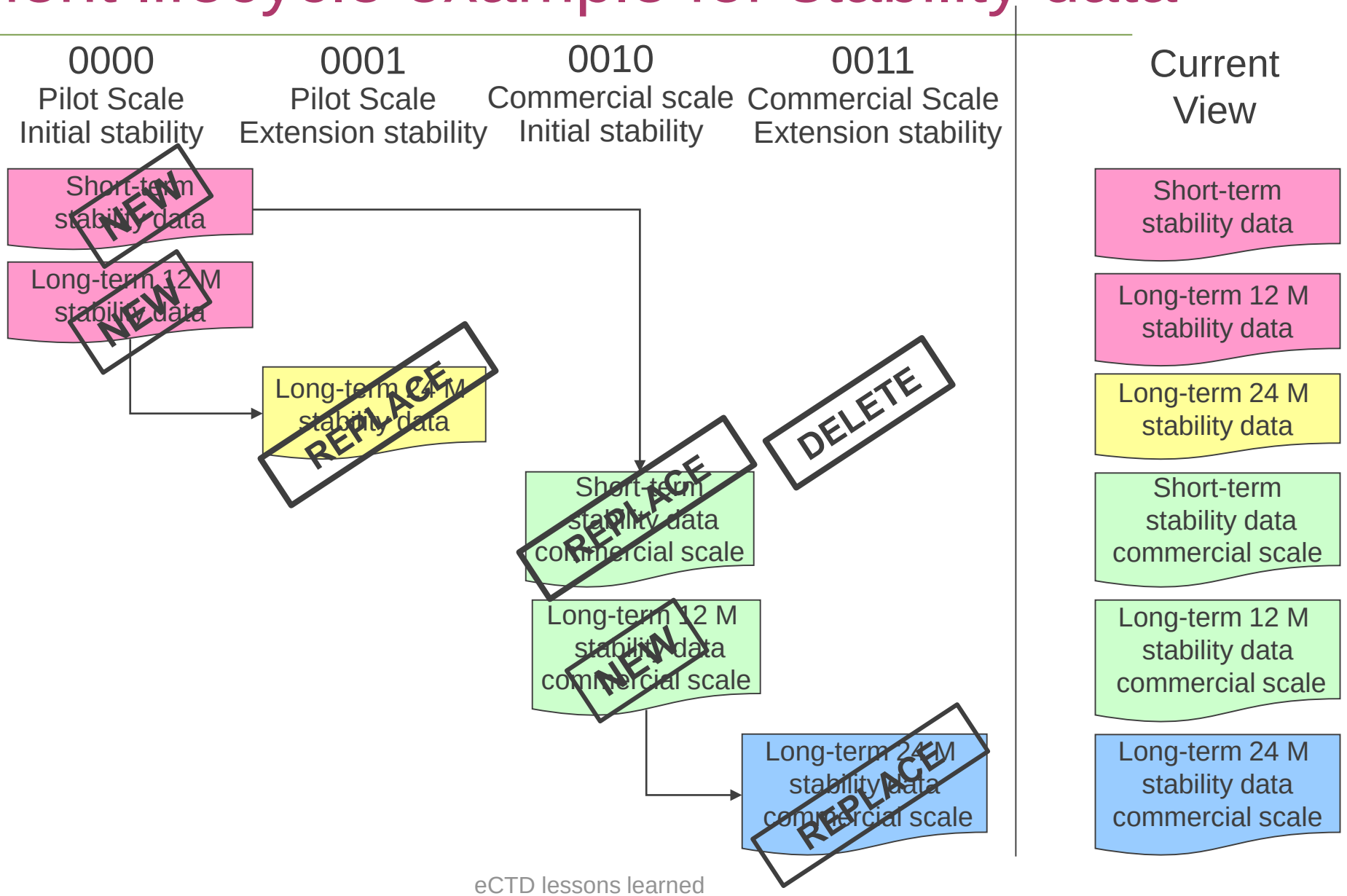
# Document lifecycle example for product information




Current View

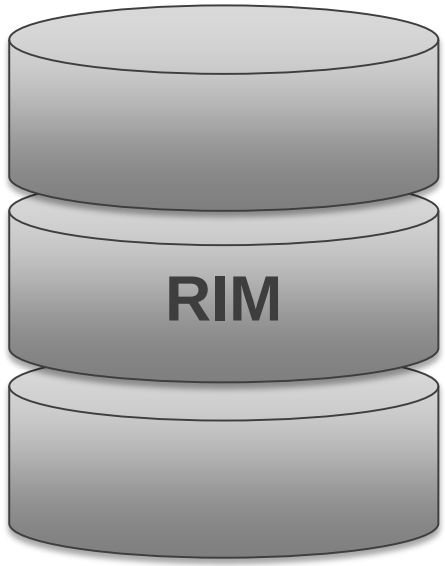
- Proposed
- Updated proposed
- Approved
- Proposed additional indication

# Document lifecycle example for stability data

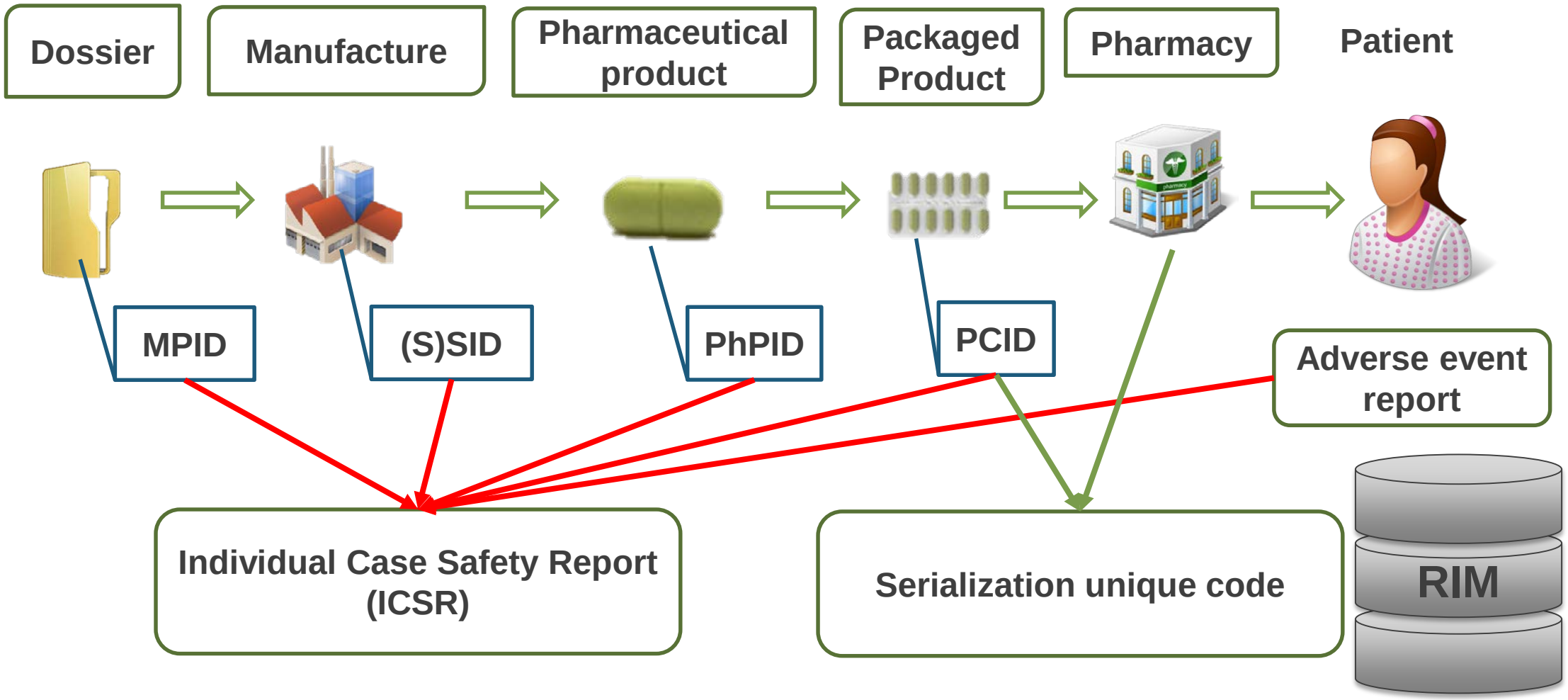


# Data lifecycle

- Extended Eudravigilance Medicinal Product Dictionary (XEVMPD)
  - To be able to attribute adverse events to, amongst others
    - Product
    - Formulation + strength
    - Substance
    - Indication
- Serialization
  - To protect against falsified medicine, linking to, amongst others
    - Manufacturer
    - Packaging
- Identification of Medicinal Products (IDMP)
  - As for XEVMPD and Serialization, but more details such as
    - Specified substance
    - Contraindications
    - All organizations involved
    - Etc.

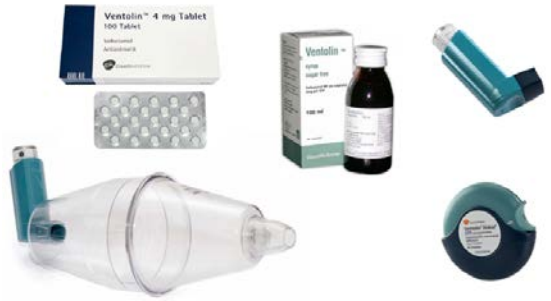


# Identifiers used in Life Science and Healthcare

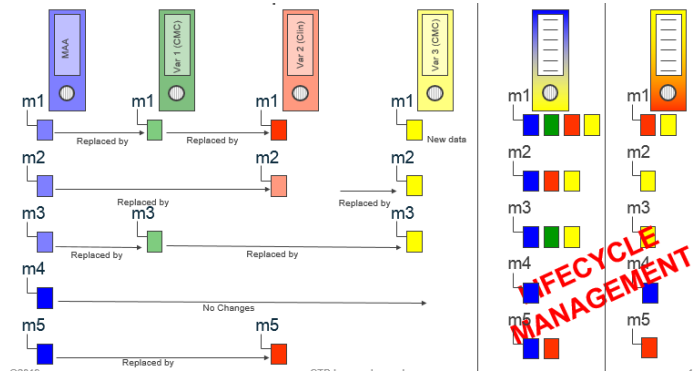


# Lifecycle on information on …….

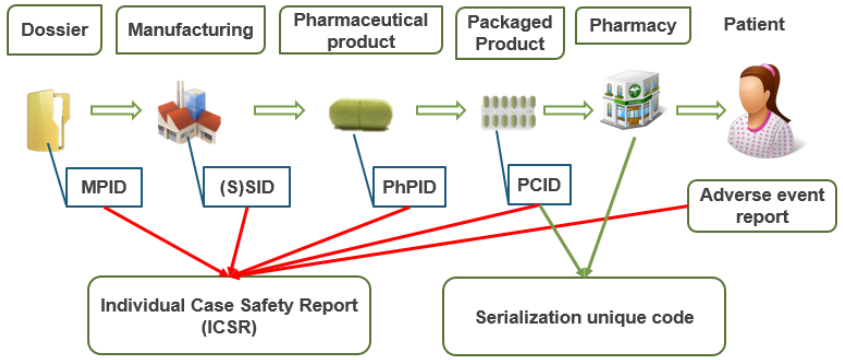
- Products




- Dossiers & Documents




- Data

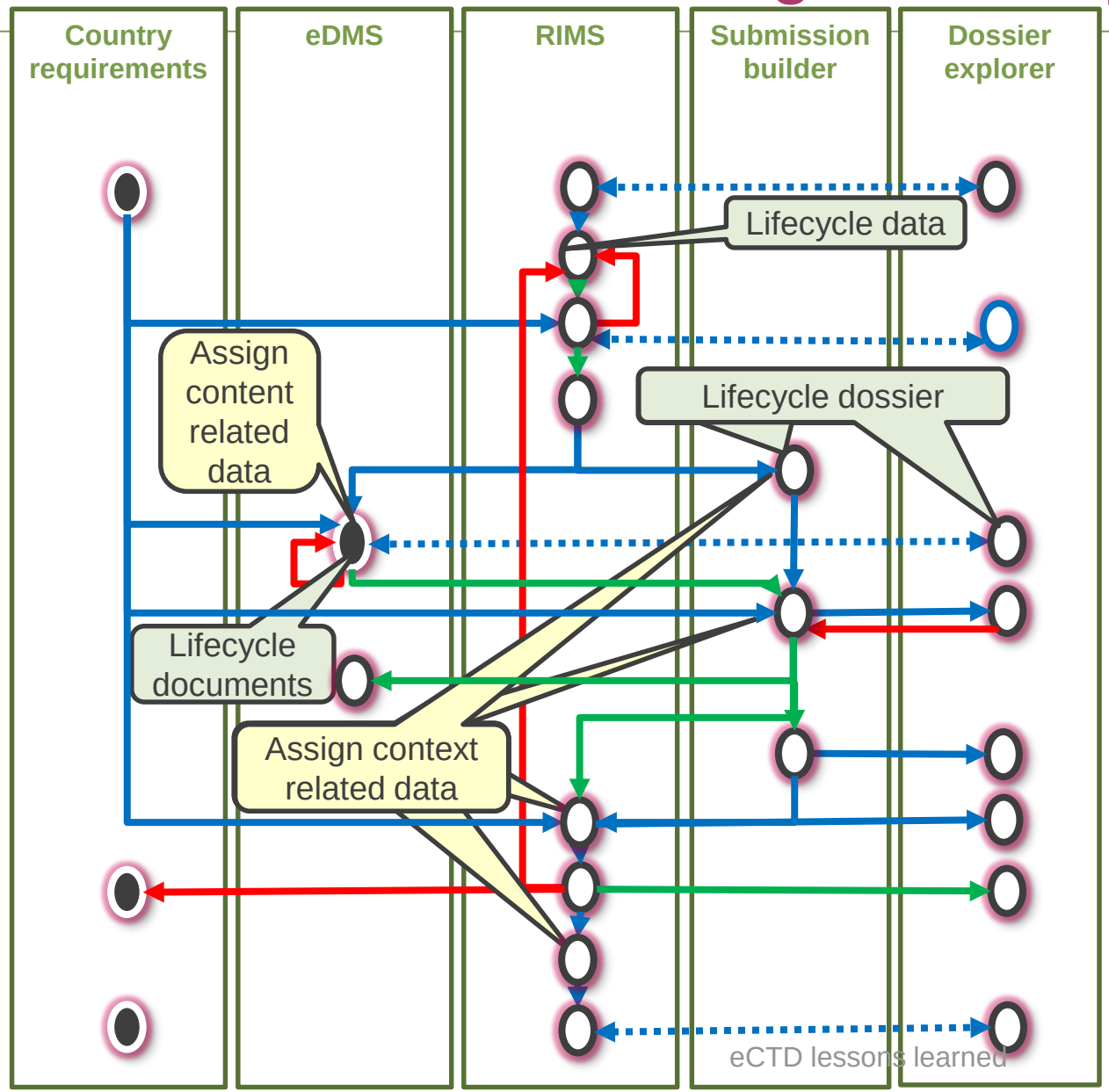


# Circular information management

# Connection of the relevant data and tools

| Required tools and databases | Ability to |
|---|---|
| Country requirements database | Know what to provide when and how to get approval for a change |
| Electronic Data Management System (eDMS) | Manage electronic documents providing proof of Quality, Safety and Efficacy of a drug |
| Regulatory Information Management System (RIMS) | Register the registration status of drugs, using company preferred terms, synonyms, codes and translations |
| Submission Builder | Compile and submit regulatory dossiers from documents (from eDMS) and data (from RIM) |
| Dossier Explorer/Viewer | Explore regulatory dossiers, across<br>- Entire lifecycle<br>- Products<br>- Countries |

# Circular information management – process and tools




- Status quo
- Release change request
- Impact assessment
- Promote to submission request
- Submission outline
- Review and release documents
- Review and release submission
- Archive submission
- Notify local affiliates (if applicable)
- Submit to health authorities
- Register agency feedback
- Batch Release to a named country
- Status quo

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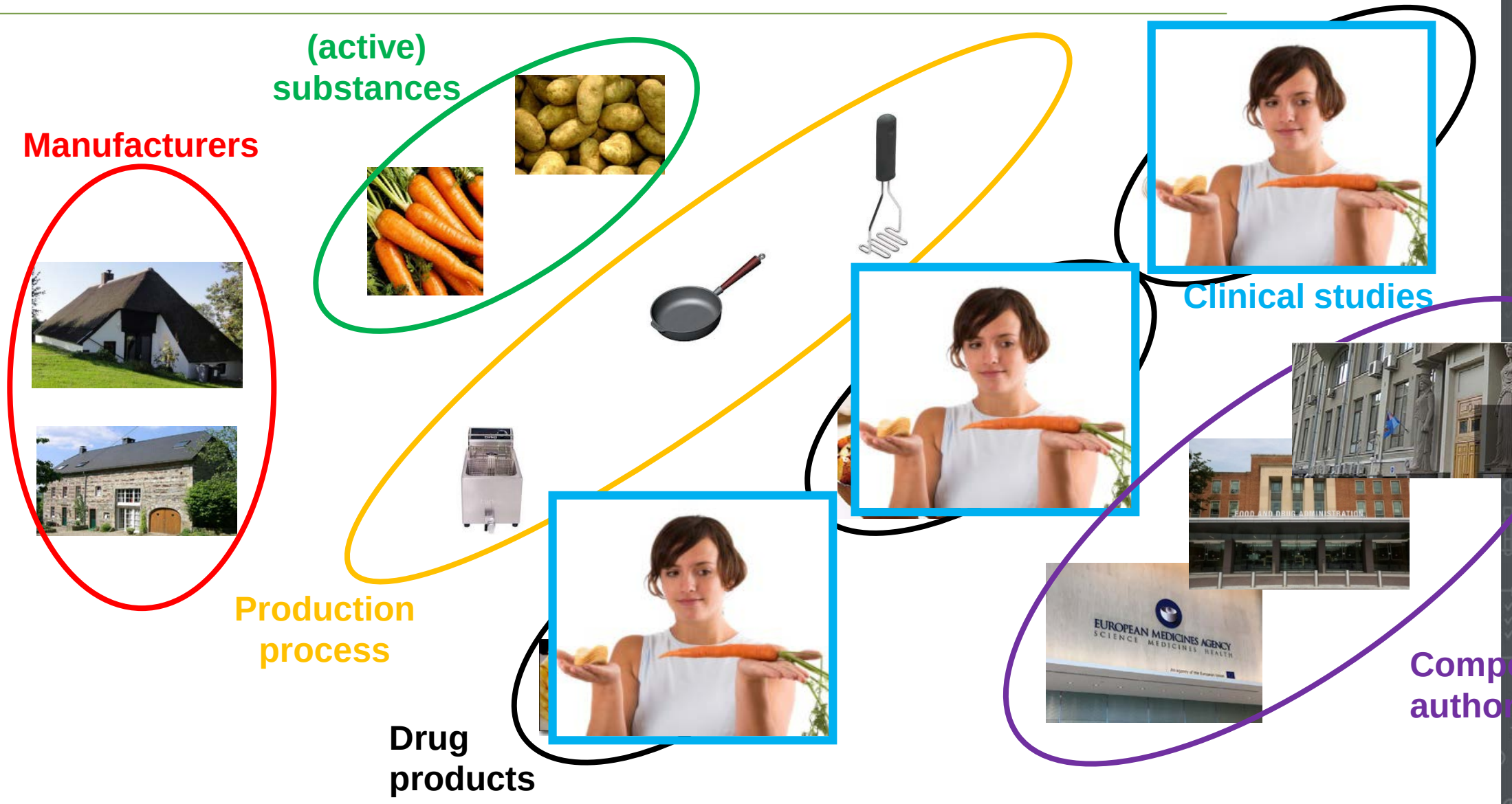
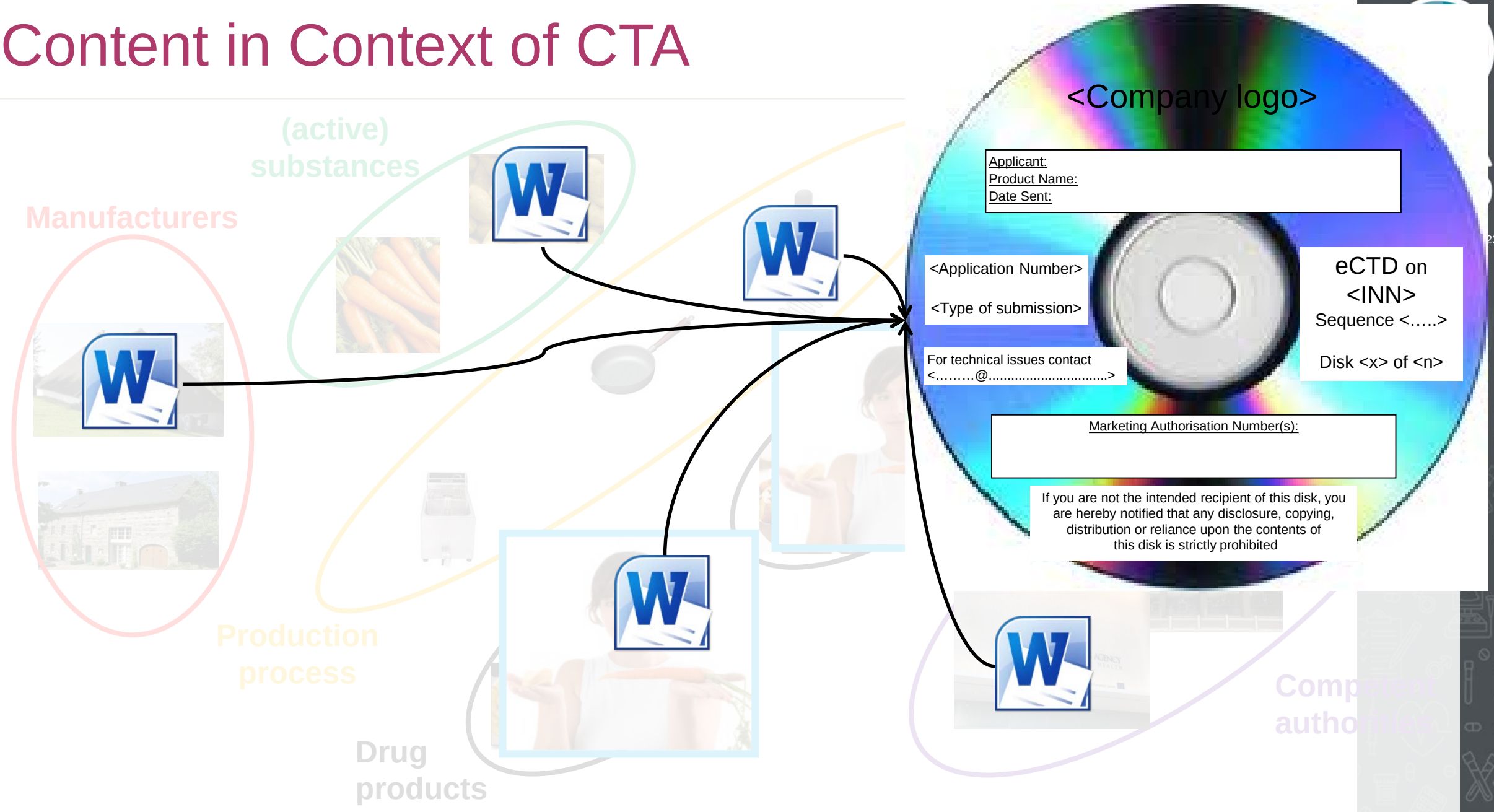
# Separate content from context

# Content vs Context - carrot and potato recipes



# Content in Context of CTA



# Content in Context of MAA


Therefore omit context from the content (e.g. Appendix, number, reference to meetings)

# Document granularity

- 32P33 Description of manufacturing process and process controls


32P33 Description of manufacturing process and process controls

  - Flow chart
  - Formulation
  - Filling
  - Labeling
  - Packaging

- 32P33 Description of manufacturing process and process controls


Flow chart


Formulation


Filling


Labeling


Packaging

# How does the EAEU eCTD fit in this?

# EAEU eCTD – the XML backbone behind the dossier

## The XML backbone (eCTD)

*What the computer reads*

R0.017

- Brand
- Company name
- Agency
- Submission date
- Regulatory activity name
- Submission type
- Sequence

R0.022

- Inclusion XMLs per document heading
  - Document title
  - Operation (new, replace, delete)
  - PDF or link to PDF
  - Other descriptive content-related data, depending on document type

## The CTD

*What humans read*

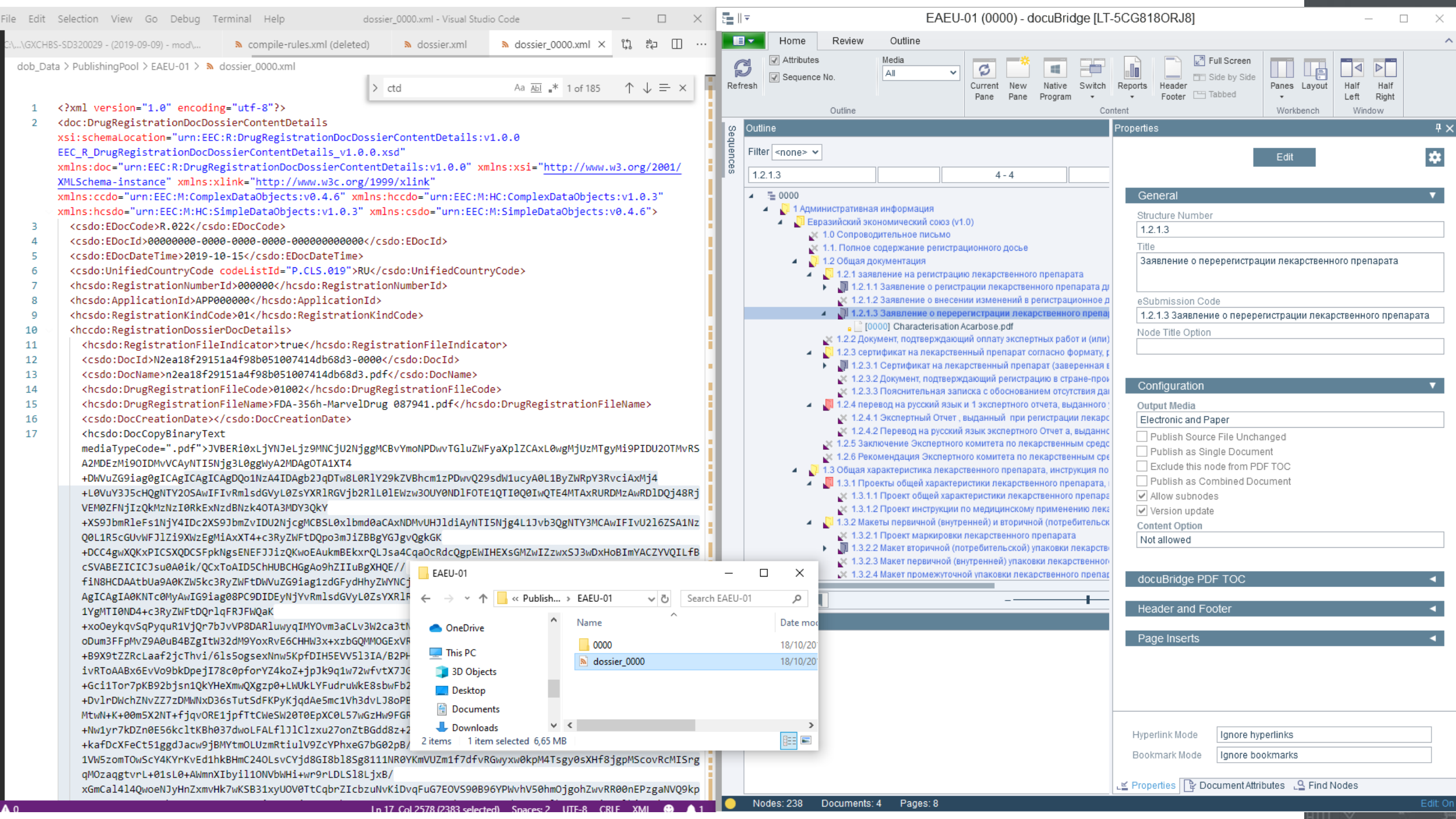
Module 1

Module 2

Module 3

Module 4

Module 5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dossier.xml
dossier_0000.xml
dob_Data > PublishingPool > EAEU-01 > dossier_0000.xml
ctd
1 of 185
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New Pane
Native Program
Switch
Reports
Header Footer
Full Screen
Side by Side
Tabbed
Panes
Layout
Half Left
Half Right
Outline
Content
Workbench
Window
Sequences
Outline
Filter <none>
1.2.1.3
4 - 4
0000
1 Административная информация
Евразийский экономический союз (v1.0)
1.0 Сопроводительное письмо
1.1. Полное содержание регистрационного досье
1.2 Общая документация
1.2.1 заявление на регистрацию лекарственного препарата
1.2.1.1 Заявление о регистрации лекарственного препарата д
1.2.1.2 Заявление о внесении изменений в регистрационное д
1.2.1.3 Заявление о перерегистрации лекарственного препа
[0000] Characterisation Acarbose.pdf
1.2.2 Документ, подтверждающий оплату экспертных работ и (или)
1.2.3 сертификат на лекарственный препарат согласно формату,
1.2.3.1 Сертификат на лекарственный препарат (заверенная к
1.2.3.2 Документ, подтверждающий регистрацию в стране-про
1.2.3.3 Пояснительная записка с обоснованием отсутствия да
1.2.4 перевод на русский язык и 1 экспертного отчета, выданного
1.2.4.1 Экспертный Отчет , выданный при регистрации лекарс
1.2.4.2 Перевод на русский язык экспертного Отчет а, выданно
1.2.5 Заключение Экспертного комитета по лекарственным средс
1.2.6 Рекомендация Экспертного комитета по лекарственным сре
1.3 Общая характеристика лекарственного препарата, инструкция по
1.3.1 Проекты общей характеристики лекарственного препарата,
1.3.1.1 Проект общей характеристики лекарственного препара
1.3.1.2 Проект инструкции по медицинскому применению лека
1.3.2 Макеты первичной (внутренней) и вторичной (потребительск
1.3.2.1 Проект маркировки лекарственного препарата
1.3.2.2 Макет вторичной (потребительской) упаковки лекарств
1.3.2.3 Макет первичной (внутренней) упаковки лекарственно
1.3.2.4 Макет промежуточной упаковки лекарственного препа
Properties
Edit
General
Structure Number
1.2.1.3
Title
Заявление о перерегистрации лекарственного препарата
eSubmission Code
1.2.1.3 Заявление о перерегистрации лекарственного препарата
Node Title Option
Configuration
Output Media
Electronic and Paper
Publish Source File Unchanged
Publish as Single Document
Exclude this node from PDF TOC
Publish as Combined Document
Allow subnodes
Version update
Content Option
Not allowed
docuBridge PDF TOC
Header and Footer
Page Inserts
Hyperlink Mode
Ignore hyperlinks
Bookmark Mode
Ignore bookmarks
Properties
Document Attributes
Find Nodes
Nodes: 238
Documents: 4
Pages: 8
Edit: On

# eCTD lifecycle in practice

# When to mandate eCTDs?

- Mandate experiences from the EU
  1. New MAAs in Centralized Procedure
  2. New regulatory activities in CP
  3. New MAAs in MRP/DCP
  4. New regulatory activities in MRP/DCP
  5. New MAAs in National applications
  6. New regulatory activities in National applications
- Mandate experiences from the EU
  - Baselines / reformats encouraged, but not mandated
    - Proper base lines are time consuming and impact content more than format
    - Electronic paper does not add value over paper, other than transfer.
    - Baselines are a new start for proper lifecycle

# Advantages of eCTD lifecycle management and attribution of the correct metadata – an illustration

- Was a particular adverse event labeled or unlabeled in the product information at the time the AE was reported?
  - Snapshot view on PI
- In which countries have I used the Manufacturer ‘Waalwijk’ where I have findings with my audit?
  - View across dossiers and show manufacturer
- For which products do I have to update the quality standard about Excipient ‘Magnesium stearate’?
  - View across dossiers and show excipient
- What is the current status of the specifications of ‘ProduQt’ in ‘EU MRP’?
  - Current view ProduQt’ in ‘EU MRP
- What stability duration has been submitted where?
  - See Oman, Thailand and EU MRP example

eCTD viewer

# eCTD validation criteria

Beyond and above what is mandated

# Purpose of validation

- To assure that what has been submitted is fit for review by the validating agency

# Technical vs. Business validation

- Can technically be processed by agencies
  - Does the reviewer see what is intended by the applicant?
    - Now
    - In the future
- All data available to examine quality, safety and efficacy
  - Now
- Are the current view of the dossier and the actually marketed product aligned
  - Regulatory compliance!!!!

So there is more than just technical validation per sequence

# Technical validation criteria

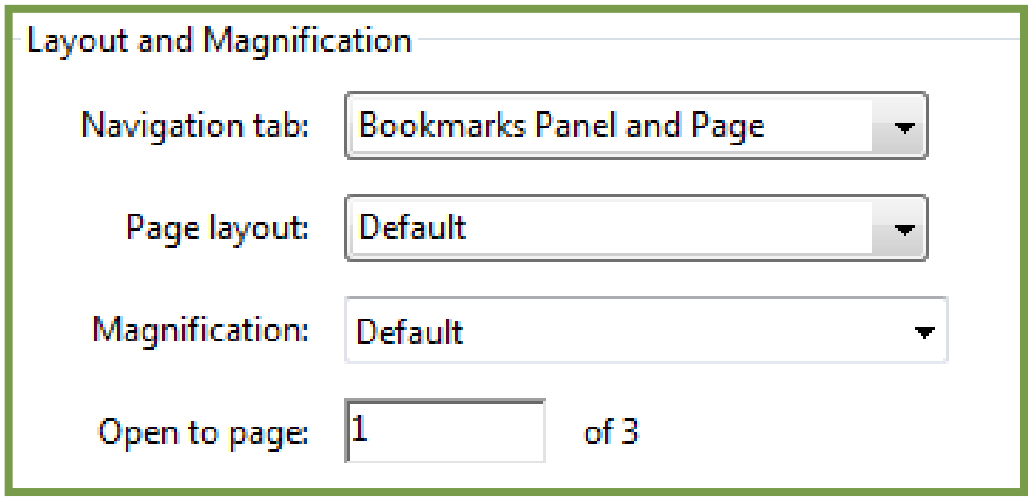
- According to EU Validation Criteria v7.1
  - Included “common sense” checks
  - Included consistency checks
- Based on ICH Q36
- EU eCTD technical validation criteria tested by
  - eXtedo EURS is YOURS validator (EMA and majority EU MSs)
  - Lorenz validator (DE, AT, SI,…)
- Statement on virus protection in the ‘Cover letter’
- Deviations can be clarified in the ‘Note to reviewer’

What are the detailed EAEU validation criteria?

What tools can test this?

# eCTD readiness of PDF documents

- Must be PDF 1.4 or higher
  - Preferably higher
- Initial view (BMP&P, default, default)
- Magnification of bookmarks and links: Inherit Zoom
- Fast web view enabled

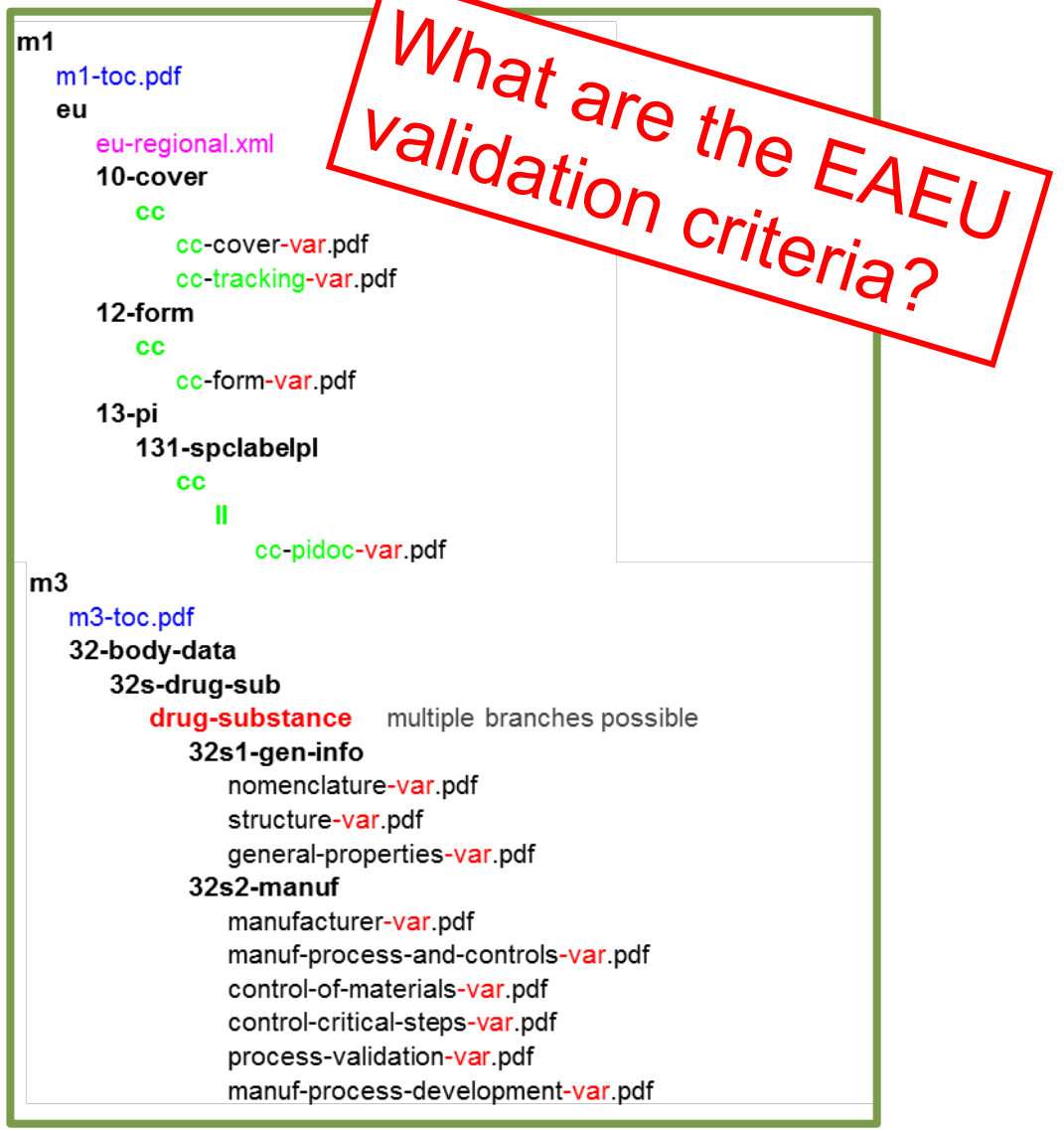



- Hyperlinks have valid destinations
  - Within documents
  - Between documents

# Colour legend for file and folder naming

Fixed parts for folder and file names:

- Variable parts for folder and file names, multiple files are accepted
- Pick list values according to the EU specification
- File names only applicable for NEES
- Folders and file names only applicable for eCTD



# Technical EU eCTD validation criteria

- Included “common sense” checks
- Included consistency checks
- Build on top of ICH Q&A
- Pass/Fail (P/F) criteria must be met
- Best Practice (BP) criteria should be met
  - if not → explain in the Cover letter / Note to reviewer
- File name
  - P/F for NEES
  - BP for eCTD

Consider a note to reviewer document to address B/P deviations?

# ‘Common sense’ checks - 1

- Cover letter- and Application form-data reflected correctly in the envelop
  - Sign off cover letters and application forms by the one in the Letter to communicate on behalf of….
  - Correct procedure #, including regulatory activity type and sequential #
    - EMEA/H/C/002388/**IB/XXXX**; including the variable part!
    - EMEA/H/C/**0909/PSUR**; for PSUSA with # PSUSA/00000533/201405
  - Only variation mode (Single, Grouping or Worksharing) if it is a variation!
- Consistent use of metadata across CL, AF and envelop
  - Sequence # and related sequence #
  - Procedure number
  - Submission type
  - Submission description
  - Region/country

# ‘Common sense’ checks - 2

- Use of meaningful titles; e.g.
  - Proof of Payment vs. Annex 5.2
  - Note to Reviewer vs. Annex 3
  - Stability Data Long Term Stability 24 M vs. Stability Data 1
- Use of meaningful file names; e.g.
  - de-form-proofpayment.pdf vs. de-form-5.pdf
  - es-cover-notereviewer.pdf vs. es-cover-3.pdf
  - stability-data-longterm24m.pdf vs. stability-data-1.pdf
  - analytical-procedure-identityelisa.pdf vs. analytical-procedure-1.pdf

# Consistency checks

- Consistency in attribute values
  - Across documents
    - Sequence # and related sequence #
    - Procedure number
    - Submission type
    - Submission unit
    - Submission description
    - Region/country
  - Across sequences
- Correct attributes, file names and folder names within a sequence
  - Country codes
  - Language codes
  - PI Doc types

# Review of business validation criteria

- Are all data and documents included to allow for evaluation of quality, efficacy and safety?
- Administrative
  - Cover letter
  - Application form if applicable
  - Proof of payment
  - Manufacturers (names, addresses and roles)
  - Etc.
- Scientific
  - Complete data package to support the application
  - Justification for any missing data that would normally be expected
    - Clinical- and Nonclinical Overviews
    - Note to reviewer

# Follow-up unacceptable technical issues

- Inability to upload the sequence to the review tool
- Upgrade the existing sequence
- Type of submission is identical to that of the invalid sequence

Resubmit using the same sequence number within the validation period

# Follow-up unacceptable business issues

- Sequence has been uploaded to the review tool
- Create an additional new sequence using the next available sequence number
- Submission type = initial MAA
- Submission unit = response
- Note that the first sequence in this regulatory activity must be mentioned as “related sequence” in any supplemental information

Submit additional new sequence within the validation period

# Validation errors that could be prevented

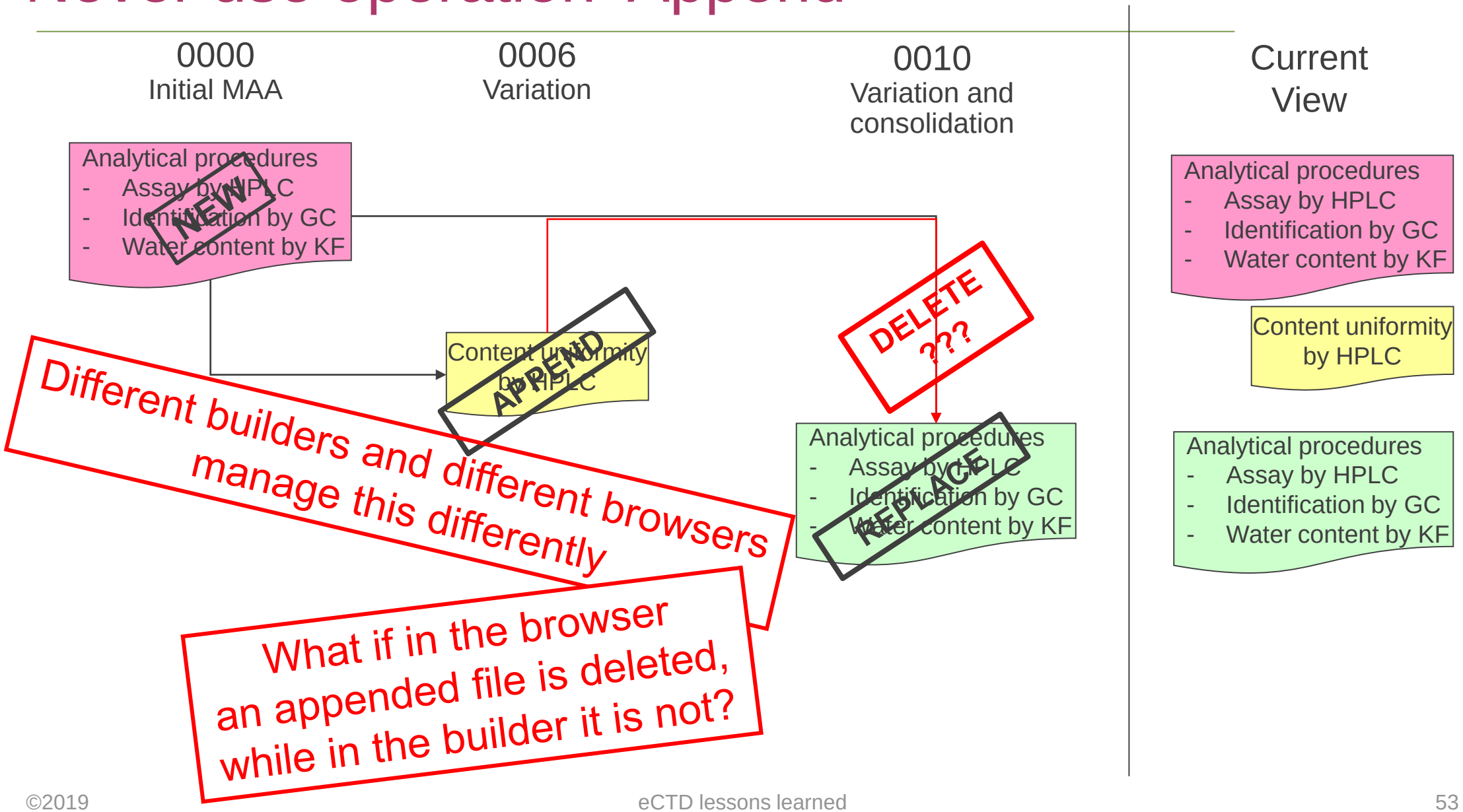
- Ensure that the same metadata is used within a sequence
  - Cover letter
  - Application form
  - Envelope information (EAEU: R.017)
- Ensure that the same metadata is used across sequences
  - Envelope information (EAEU: R.017)
- Do not store your eCTD at too low a level on a file share
  - A link URL should <256 characters for path, document name + mime type
  - Do apply the correct and current validation criteria
  - Do ensure new sequences are located in the correct eCTD lifecycle
    - When building and when receiving

# Summary on validation

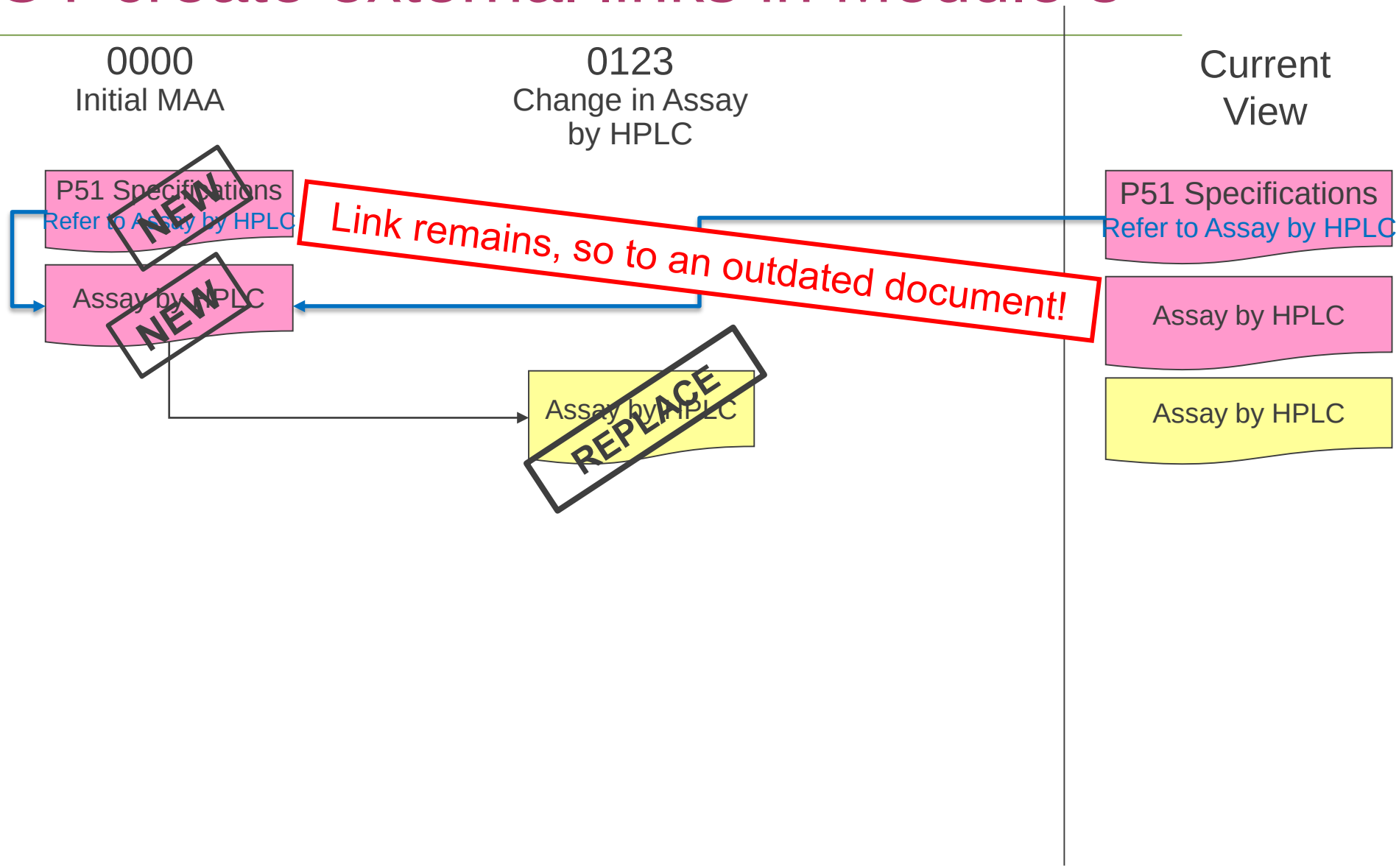
- Validation criteria are important to ensure
  - Interchangeability of dossiers
  - Future proof retrievability and readability
- Checks beyond the automated validation checks are as important
- Business validation is even more important
- Integrated set of quality checks to be implemented within each company
- Validation concerns a learning curve for industry and agencies!

# Use cases

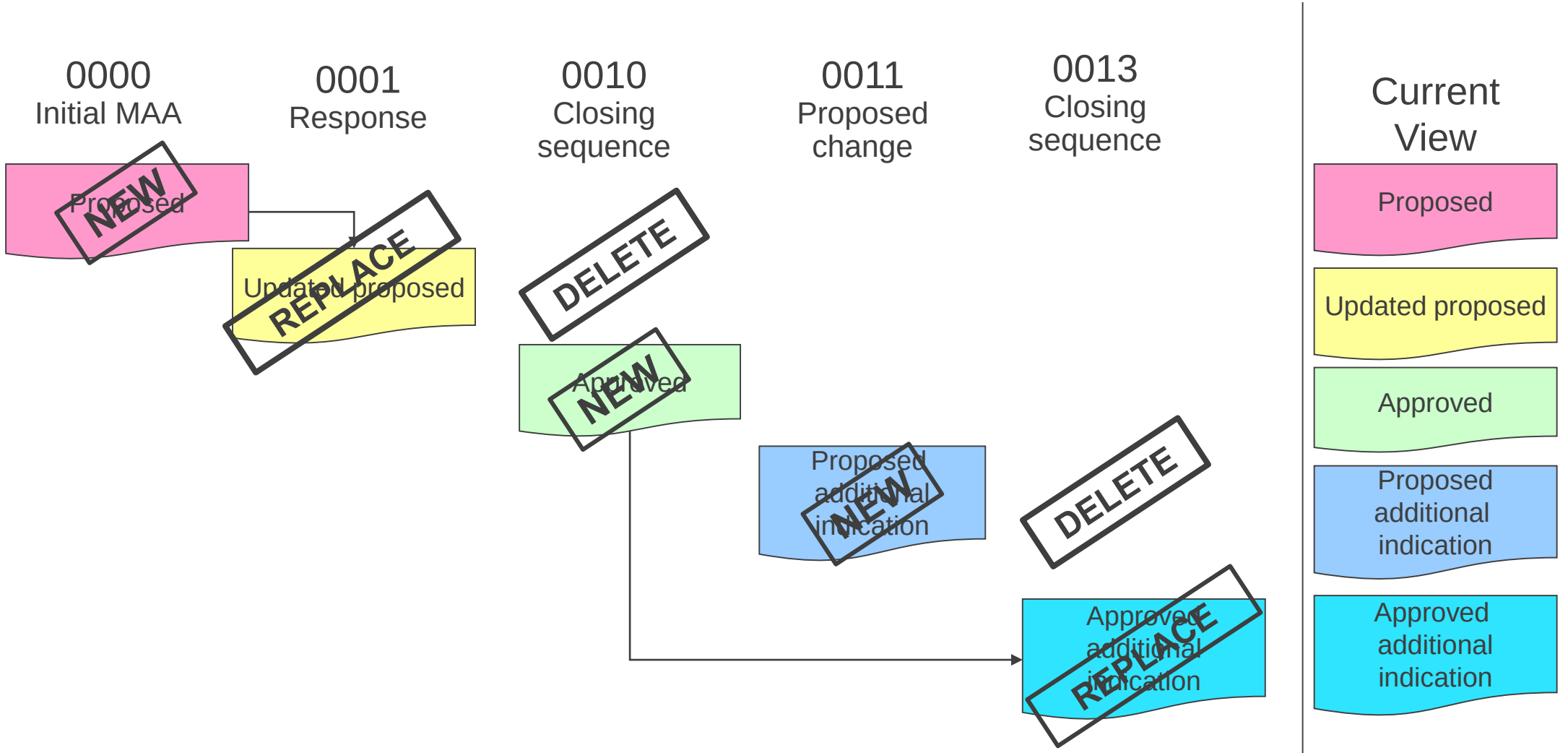
# Never use operation ‘Append’



# Do NOT create external links in Module 3



# Possible solution for normative documents!?



# Use only related sequences for supplemental information after questions

**Demo on regulatory activities**

# Import all eCTD sequences, even if not needed for each country

- Pretend that a particular sequence is not needed for CMS DE
- E.g. replacement of PL Label in MRP/DCP procedure

| NL<br>RMS | PL<br>CMS | DE<br>CMS |
|---|---|---|
| 0030 | 0030 | 0030 |
| 0031 | 0031 | ---- |
| 0032 | 0032 | 0032 |

- Some agencies do not upload sequences not applicable to them!
  - They are confronted with errors of ‘missing modified leaf’ in next sequences

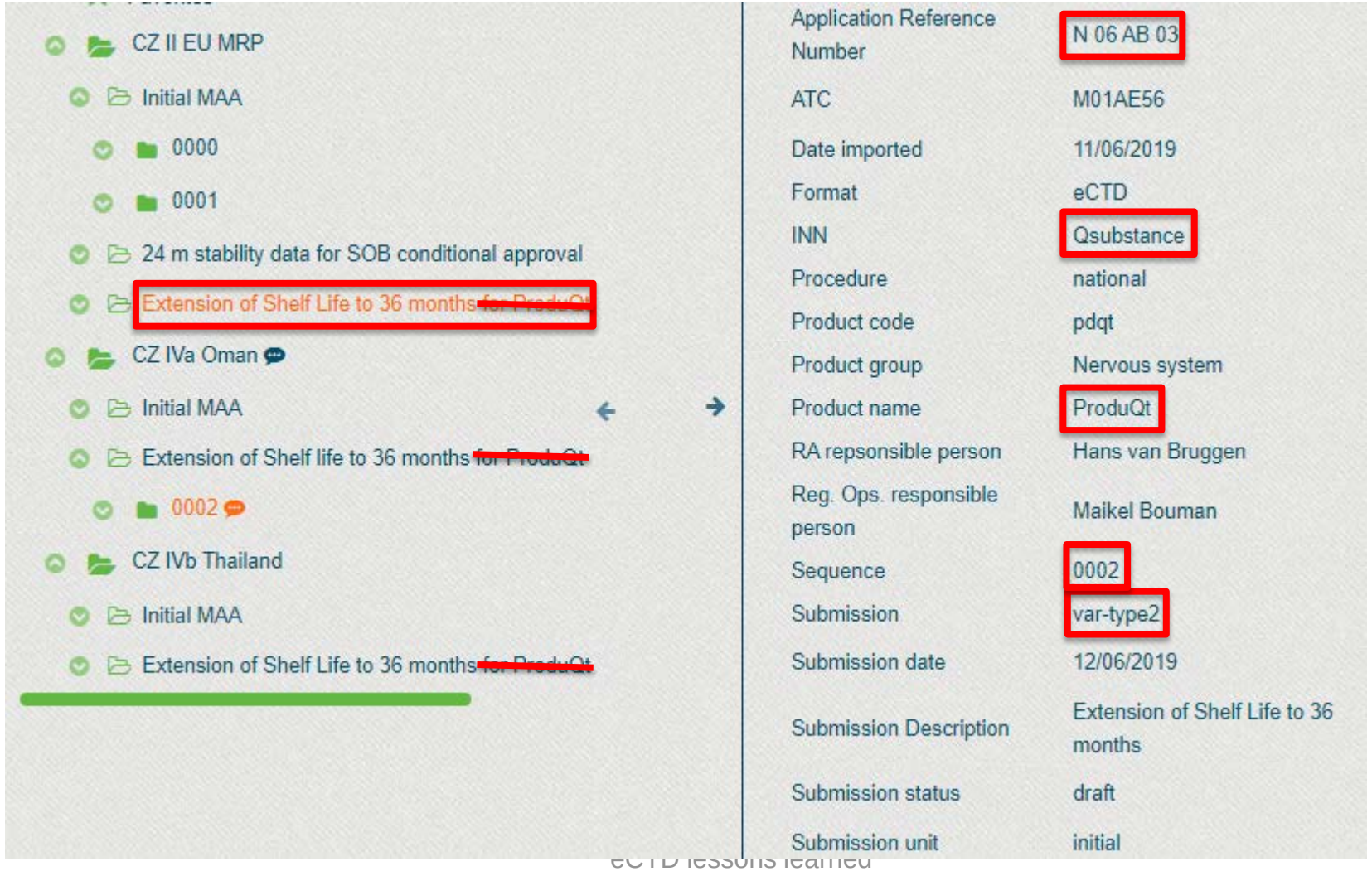
# Apply metadata within the eCTD consistently

- Do not create unintended branching


- This applies to all the metadata that is within the XML and determines the outline of the eCTD

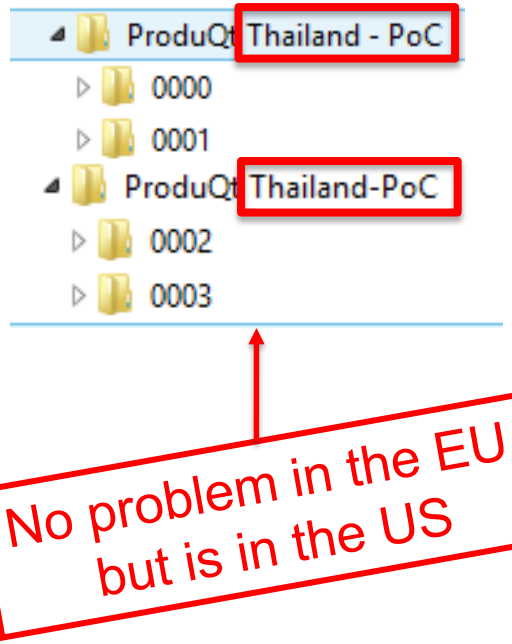
# Apply proper descriptions of regulatory activities

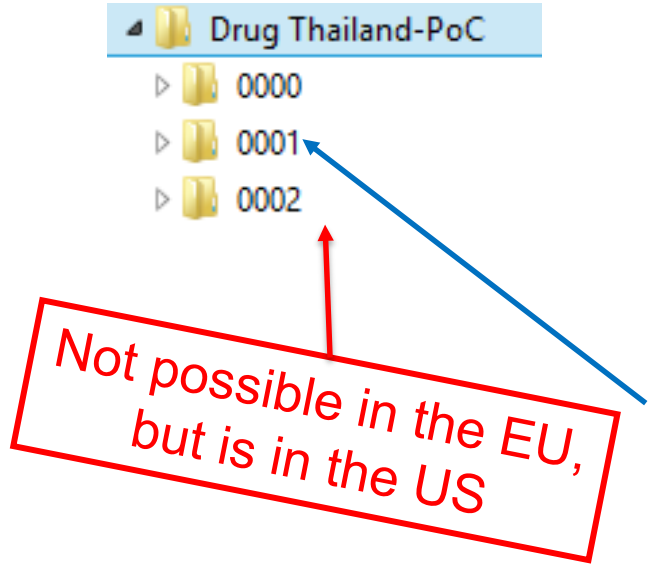
- Do not repeat information that is already in another field

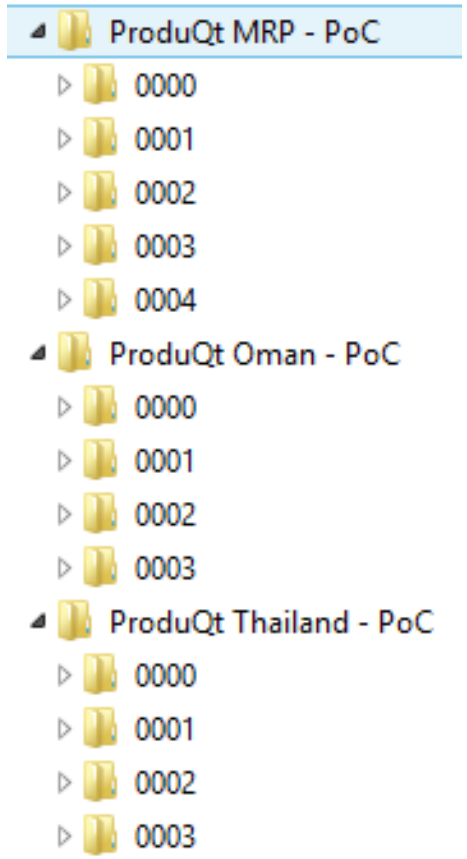


# Apply a unique root folder-name consistently

- Allows for cross dossier references
  - E.g. when using the same substance
  - E.g. when using the same CSR



# Assign future proof discriminative Module 3 metadata

- 32S per active substance
- All strengths in one 32P or separate?

- All manufacturers in one 32S or 32P or separate?

- All excipients in one 32P4 or separate?

**Demo metadata usage**

# Split large PDFs where needed

- US: individual files should not exceed 400 MB (except for data-sets)
- EU: individual files should not exceed 200 MB in size (BP)
- Belarus: individual files should not exceed 72 MB in size

- For bigger PDFs:
  - Split the document in a logical way (e.g. Appendices separate, section 14 separate)
  - Do not split artificially at the limit

# Use cases

- Never use operation ‘Append’
- Do not create external links in Module 3
  - Subject to change
  - Links will point to original and outdated information once the destination document is replaced
- Use only related sequences for supplemental information after questions
- Apply metadata within the eCTD consistently
  - Do not create unintended branching
- Apply proper descriptions of regulatory activities
  - Do not repeat information that is already in another field
- Apply a unique root folder name consistently
  - Allows for cross dossier references

# Prevent the following pitfalls

- Controlled vocabularies in dtds or schemas
- Lack of dossier lifecycle
  - No regulatory activity description
  - Incorrect related activity
  - Incorect submission type
- Lack of interoperability across tools
- Paper thinking in an electronic environment
- Technical validation issues is not prohibiting business invalid dossiers
- Ensure Module 3 always represents what is approved (allows for omitting Normative Documents)

# Summary

- The eCTD is just the carrier of regulatory information
  - Data
  - Documents
  - Dossiers
- Separate content from context
  - Create standalone reusable content
    - Documents described by content-related data
  - Put in context of use
    - Dossiers to suporrt a purpose, described by context-related data
- Apply eCTD lifecycle correctly
  - Data, documents and dossiers

Eases regulatory compliance throughout a product lifecycle across countries, companies and products