



# **Orientation Material for M8: eCTD EWG eCTD v4.0 Implementation Package v1.4**

International Council on Harmonisation of Technical  
Requirements for Pharmaceuticals for Human Use

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# Document History

June 2016	First release based on the Implementation Package v1.1
November 2016	Updated based on the Implementation Package v1.2
October 2018	Updated based on the Implementation Package v1.3
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# Table of Contents

1. Objectives of this presentation
2. Concepts and Benefits
3. Transition from v3.2.2 to eCTD v4.0
4. Region-specific Topics
5. Advantages of eCTD v4.0



# 1. Objectives of this presentation

# 1.1 Objectives of this presentation

- Target audience
  - Business personnel and management involved in any aspect of eCTD submission design and preparation.
- Provide an overview of:
  - eCTD v4.0 concepts and benefits in plain language
  - High level considerations for transitioning from v3.2.2 to eCTD v4.0



## 2. eCTD Concepts and Benefits

## 2.1 Key Messages

- With eCTD v4.0, you can
  - Re-use documents submitted previously,
  - Correct information (e.g. display name or document title) easily,
  - Group documents within a CTD section in a consistent way across ICH regions,
  - Change document granularity while maintaining life cycle relationships,
  - Set the order of documents within a CTD section,
  - Identify submission content (e.g., datasets) for additional processing, and
  - Transition current content in v3.2.2 to v4.0 and continue eCTD life cycle in v4.0.

## 2.2 eCTD v4.0 Concepts

- a. Application/Submission
- b. Controlled Vocabulary
- c. Keywords and Keyword Definitions
- d. Context of Use
- e. Ordering Content
- f. Document Label
- g. Document
- h. Group Title
- i. Study Group Order



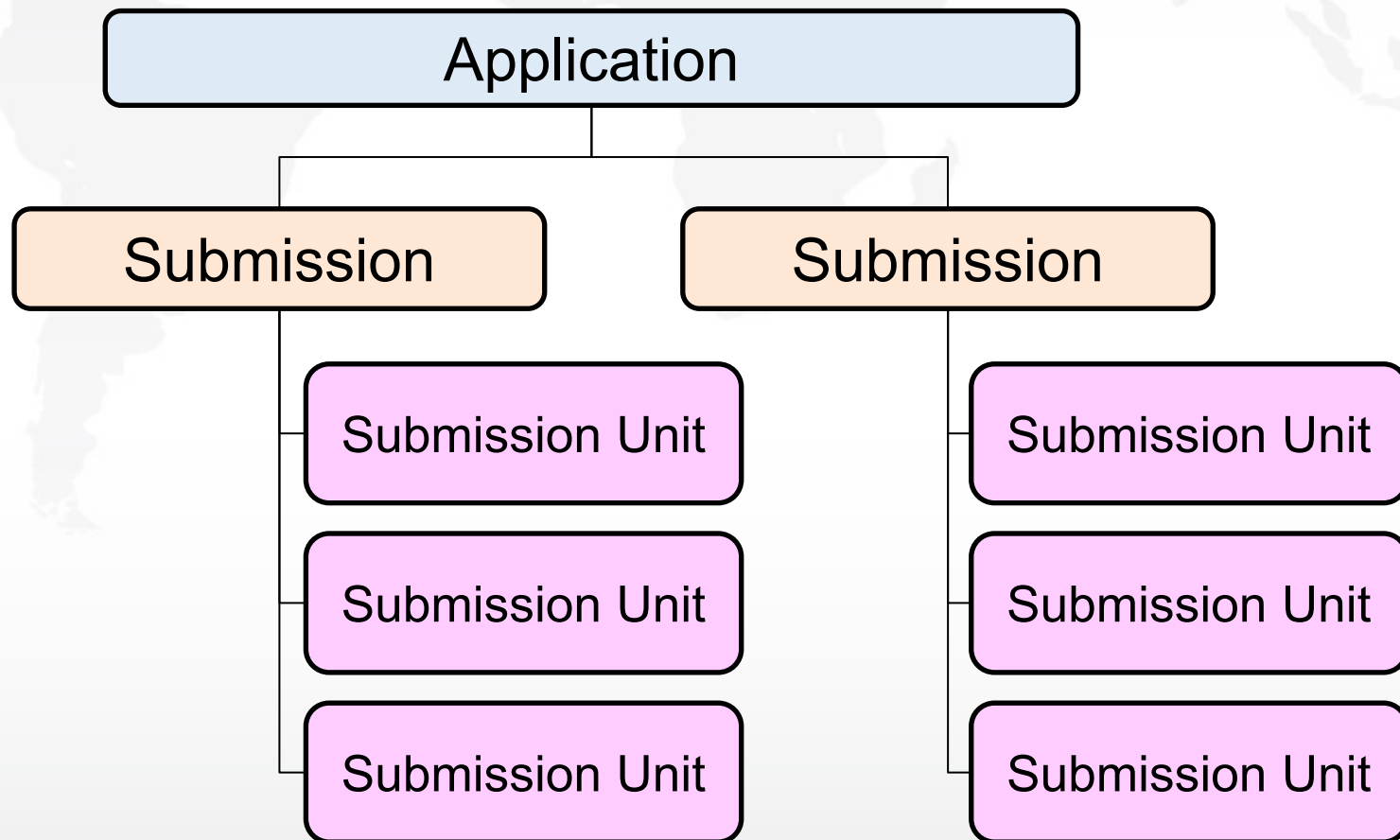
## **a. Application – Submission – Submission Unit**

## Application-submission-submission unit relationship

- The application is primarily a Module 1 concept and is described in the Regional/Module 1 Implementation Guide. In some regions it represents the concerned products with all their strengths and pharmaceutical forms as decided by the applicant to be combined within one dossier considering the most effective life cycle approach. In other regions it represents a superordinate concept that covers one or multiple products that share a common set of documents for review.
- The submission is primarily a Module 1 concept and described in the Regional/Module 1 Implementation Guide. In some regions it represents a regulatory activity such as new marketing authorisation application or renewal for that one application. In other regions it represents almost the same as the application.
- The submission unit covers all content submitted at one time point related to the submission, e.g. all required information for a new application or to respond to a list of questions during the assessment of that new application.

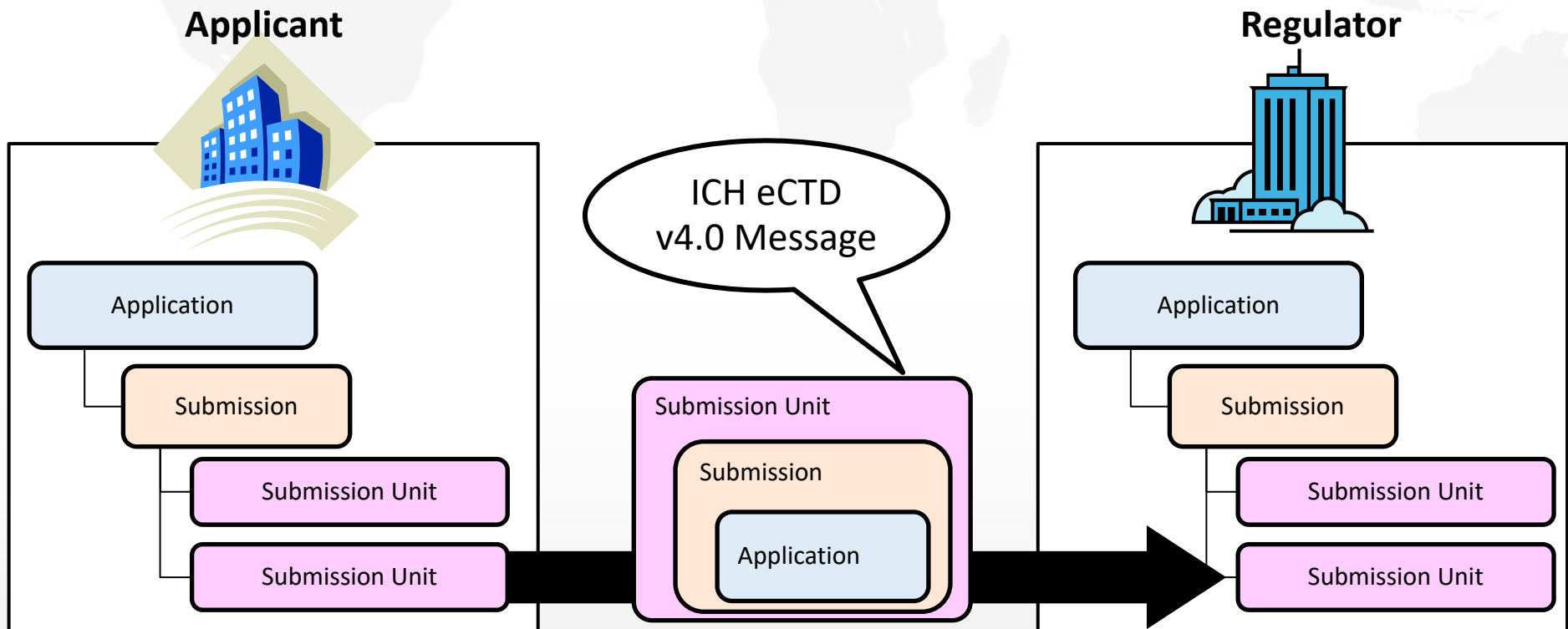
# ICH eCTD v4.0 - Big Picture

- 3-layered Structure



# ICH eCTD v4.0 – Big Picture

- Applicant submits Submission Unit to Regulator
  - A Submission Unit has the information about the Submission and Application to which it belongs.



*Note: Two-way communication is excluded from ICH business cases.*



## **b. Controlled Vocabulary**

# Controlled vocabularies (CV)

- A controlled vocabulary (CV) is a list of allowed terms for a specific concept.
- Each CV is maintained by a specific organization that establishes and updates the allowed terms.
- 5 types of CVs for eCTD v4.0
  - Specified by ICH
  - Specified Regionally
  - Specified by HL7
  - Specified by External Organization
  - Sender-defined

# Controlled vocabularies (CV)

- Examples of controlled vocabularies:
  - ICH CV for species
    - Mouse, rat, dog, etc.
  - US regional CV for application
    - NDA, IND, ANDA, BLA, etc.
- Examples of CVs that are new for v4.0
  - Category Event\* – to provide additional structured information about the submission unit contents
  - Document Types – replace file tag valid values (e.g., preclinical study report, study report synopsis)
  - Study Group Order – to provide a mechanism to order studies when the Study ID and Study Title keyword is used (refer to slide #39)

## Fewer system updates expected

- CTD or regional structure updates will be based on controlled vocabularies.
  - Allow implementation of changes to the CTD Table of Contents (TOC) and associated keywords
  - Greater flexibility to meet evolving business practices, but some system updates may be warranted
  - Business Rules may still require new logic and/or checks.
  - Updates to controlled vocabulary may require the retirement of obsolete terms.



## **c. Keyword and Keyword Definitions**

# Keyword and keyword definition

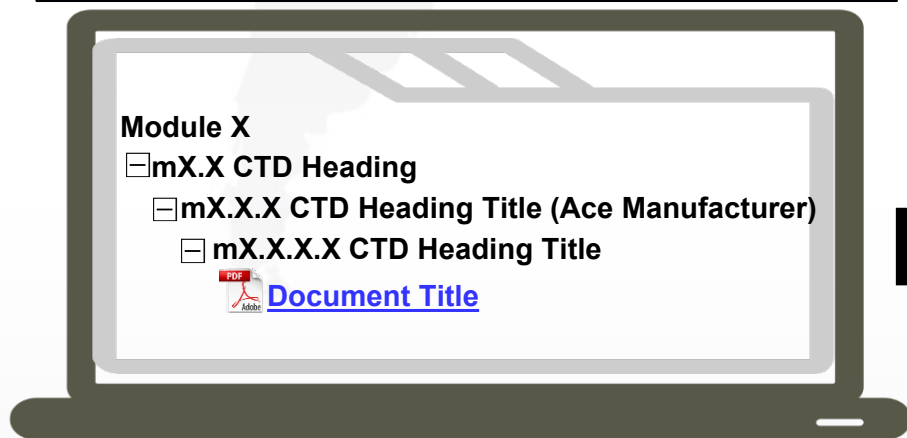
- Additional information used to organize documents within a TOC heading/section
- Keyword
  - List of allowed terms is provided (Controlled Vocabulary)
    - e.g., list of terms for “*type of control*” is defined by ICH.
  - Reference to a sender-defined keyword definition
- Keyword definition
  - Sender defines list of terms
    - e.g., company 1, company 2 for “*manufacturer*”

# Update keywordDefinition displayName

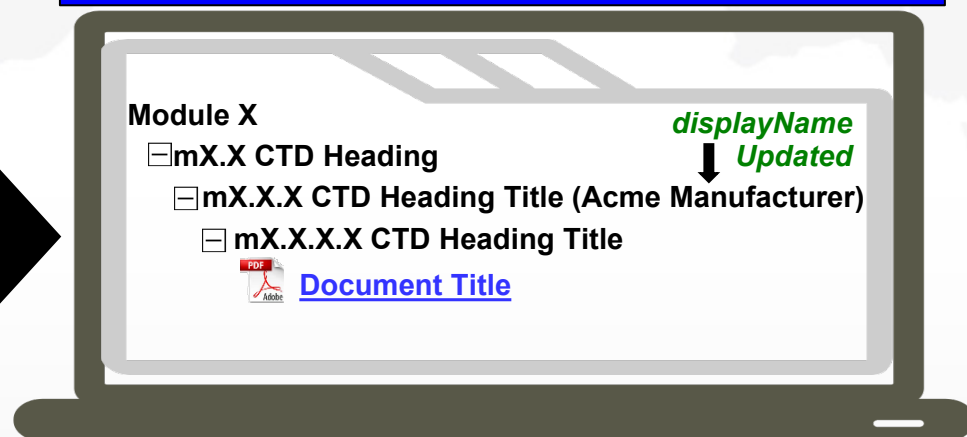
- Updates can be made for typos or errors to the displayName

Possible views on the tool

## Sequence 1



## Sequence 2



Note: ICH doesn't define any view on any tool. Tool design is at the discretion of the tool vendors.



## d. Context of Use

## Context of Use (COU)

- Placement of a document within a TOC heading/section
- Provides information regarding the usage of a document and its life cycle (e.g., content may be replaced).
- **Keyword** gives additional information to the **CoU**.
- Example:

COU X

**3.2.S.2 Manufacture** (**name 1, manufacturer 1**)

# CoU and Keyword Combinations

- The combination of **CoU** and **keyword(s)** defines the context of the submission contents. If any one of them is different, the context is considered different.

**COU X**

**3.2.S.2 Manufacture**

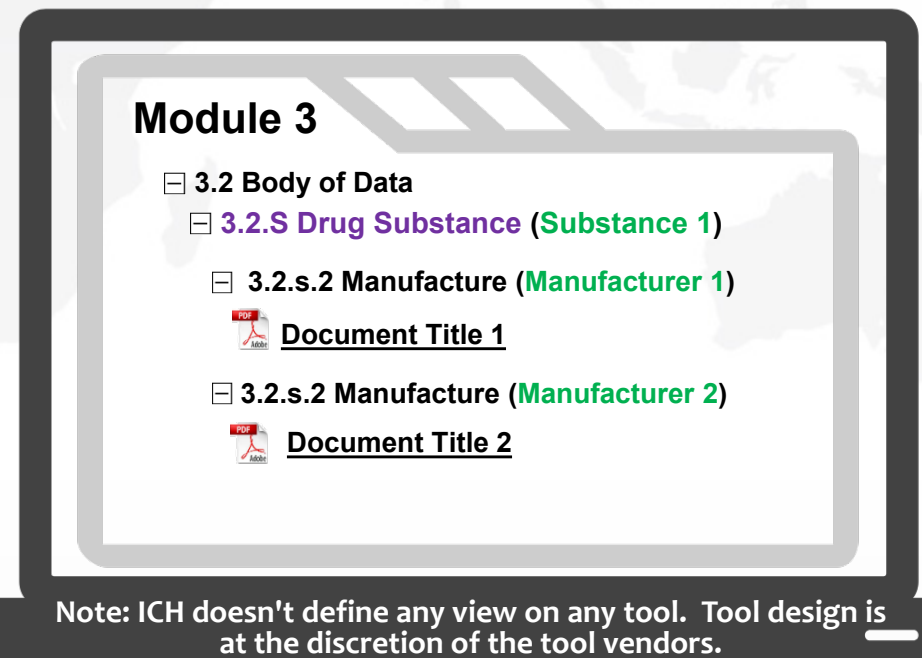
**Substance 1 manufacturer 1**

**COU Y**

**3.2.S.2 Manufacture**

**Substance 1, manufacturer 2**

Possible view in the tool



# Life cycle operators

- Active, Replace and Suspend (previously New, Replace, Delete) - valid life cycle operators in eCTD v4.0
- Append life cycle operator omitted from eCTD v4.0
  - The applicant should take into consideration the removal of the append life cycle operator when developing a strategy to manage the life cycle of documents in eCTD v4.0.

# Life cycle operator - Replace

- Replace one document with one document
- Replace one document with many documents
- Replace many documents with one document
- Life cycle relationship is maintained on all documents



## **e. Ordering Content (Priority Number)**

## Set the order of documents within a CTD section

- Using Priority number
- Explicitly define the display order of Context of Use in a specific section
- Defines the order of display for each Combination of CoU and keyword(s) in a given CTD section
- Sender may reorder submission content or insert submission content into a specific order within the existing content over time
- Similar view on end-users' screen

# Update Priority Number

Possible views on the tool

## Sequence 1

### Module X

- mX.X CTD Heading
  - mX.X.X CTD Heading Title (keyword displayName)
  - mX.X.X.X CTD Heading Title



[Document Title 1](#)



[Document Title 2](#)



[Document Title 3](#)



[Document Title 5](#)



## Sequence 2

### Module X

- mX.X CTD Heading
  - mX.X.X CTD Heading Title (keyword displayName)
    - mX.X.X.X CTD Heading Title *Order Updated!* ↓



[Document Title 5](#)



[Document Title 1](#)



[Document Title 3](#)



[Document Title 2](#)

Note: ICH doesn't define any view on any tool. Tool design is at the discretion of the tool vendors.



## f. Document Label

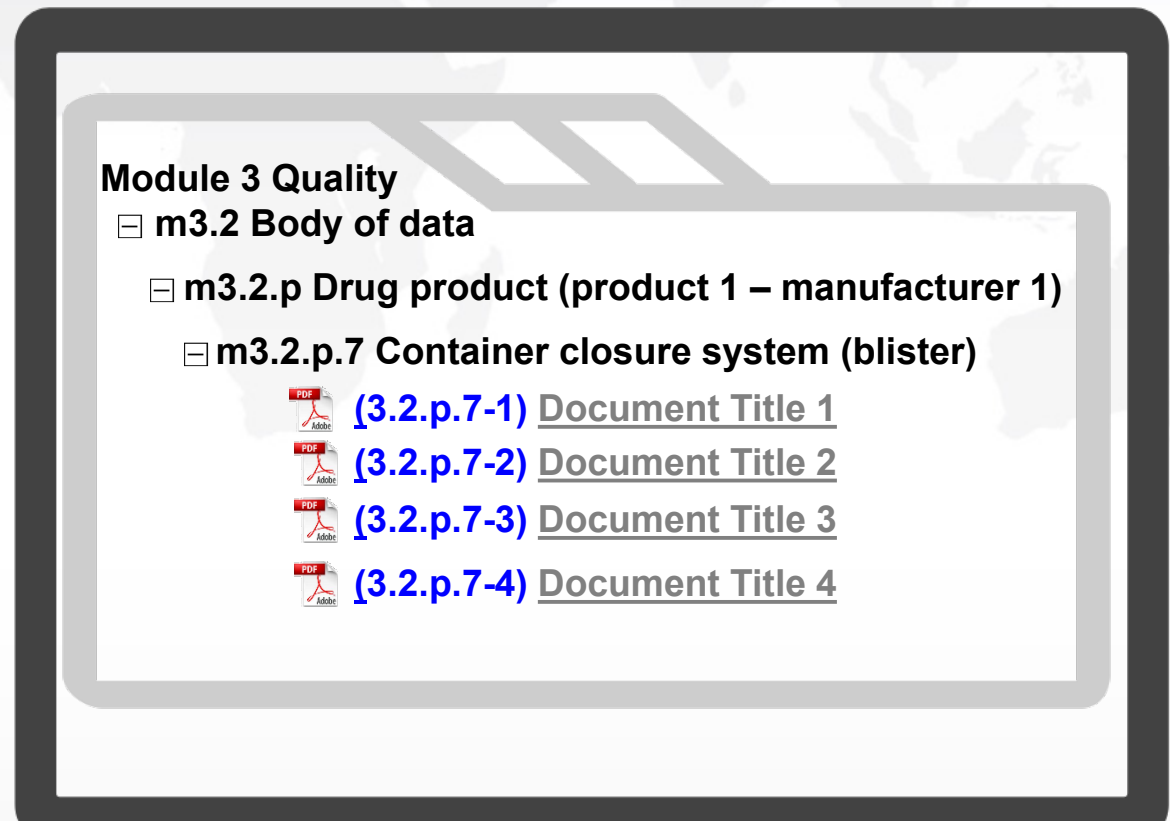
## Document Label

- Sender-defined value to abbreviate the document title
- Value is associated with the Context of Use
- Document Label addresses issues with the length or similar values given for document title
  - Document title may be too long or too generic to quickly identify contents with review staff
- Value does not impact priority number for ordering

# Apply Document Label

- Senders can use the **document label** to provide a short document name for easier reference

Possible views in the tool



Note: ICH doesn't define any view on any tool. Tool design is at the discretion of the tool vendors.



## **g. Documents**

# Reuse documents previously submitted

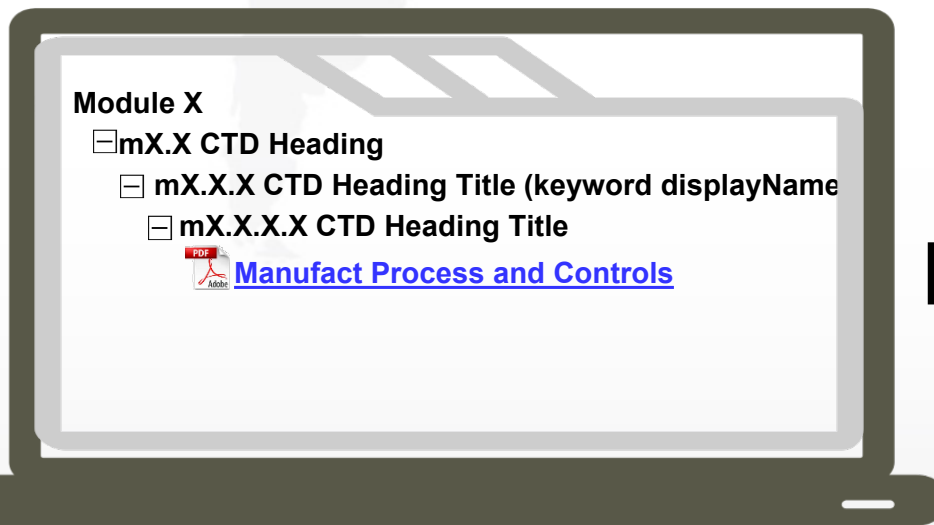
- Unique identifier approach means documents can be referenced/reused more effectively without resubmitting the physical file
  - Across a Submission Unit (Sequence)
  - Across regulatory activities within an application
  - Across different applications
- Used to reference the document in a context of use
- Reuse of document metadata (e.g., document title, language)
- Allows the reuse of documents with a reference to the identifier instead of the resubmission of the documents

# Update Document title

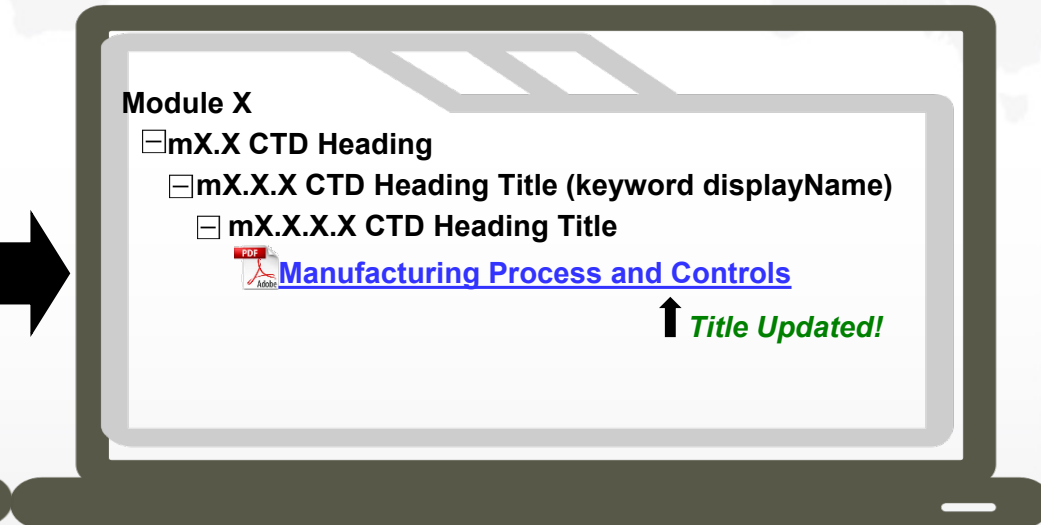
- Update keyword definition display name, document title, etc.
  - e.g., fix typo

Possible views on the tool

## Sequence 1



## Sequence 2



Note: ICH doesn't define any view on any tool. Tool's design is at the discretion of the tool vendors.



## **h. Group Title**

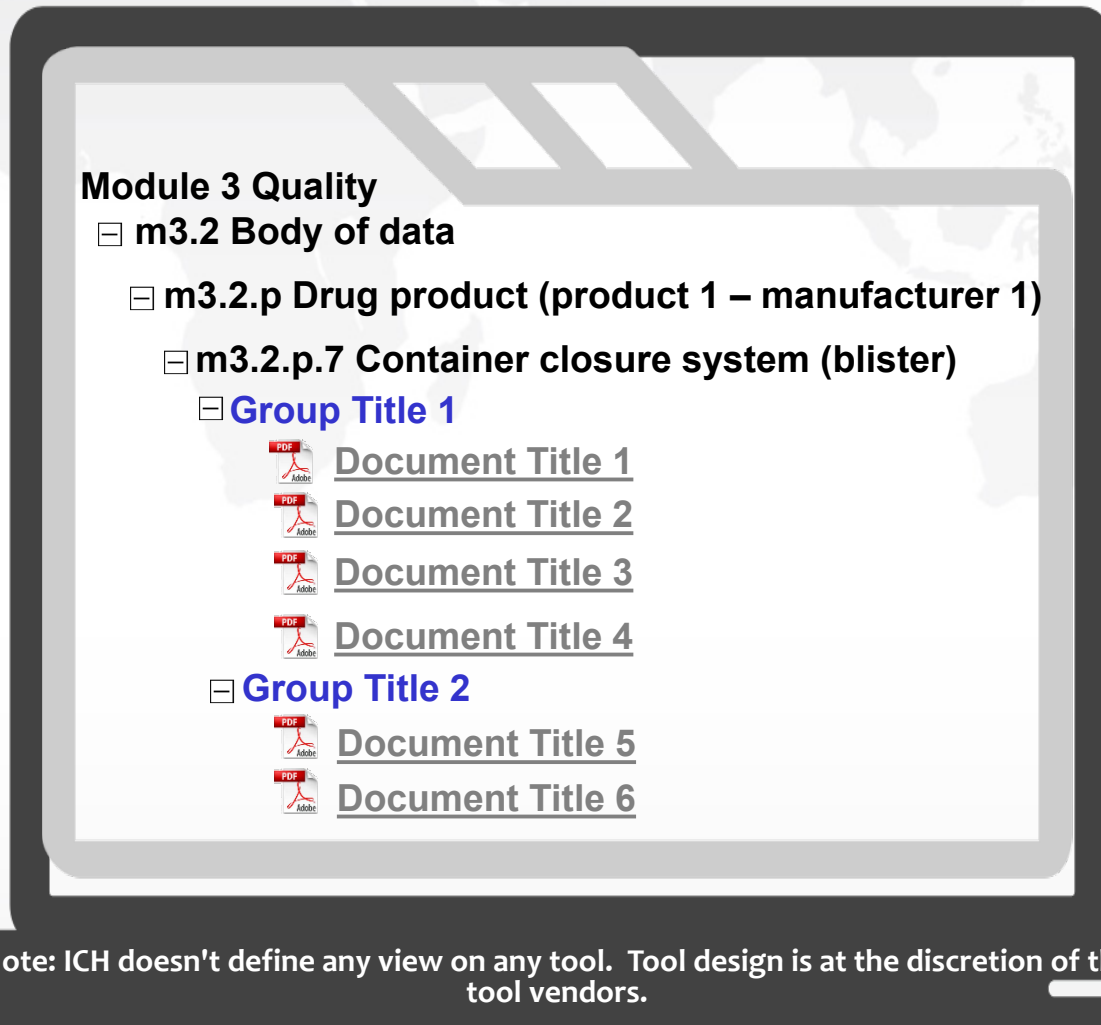
# Grouping of content in a CTD section

- Uses Group Title Keyword
- Applied to a Context of Use or Context of Use and Keyword combination to further organize content under a CTD heading when multiple documents are allowed
- The sender assigns the group title and priority number to specify how the content should appear together in a particular order

# Apply Group Title

Possible views in the tool

- Senders can use group title based on M4 Granularity Document where “One or multiple documents can be submitted”
- Replaces regional implementation of Node Extensions



The screenshot shows a tool interface with a hierarchical tree structure. The root node is "Module 3 Quality". It has a sub-node "m3.2 Body of data", which in turn has a sub-node "m3.2.p Drug product (product 1 – manufacturer 1)". Under this node, there is a sub-node "m3.2.p.7 Container closure system (blister)". This node is expanded to show two "Group Title" nodes: "Group Title 1" and "Group Title 2". Under "Group Title 1", there are four document icons (PDF Adobe) with titles "Document Title 1", "Document Title 2", "Document Title 3", and "Document Title 4". Under "Group Title 2", there are two document icons with titles "Document Title 5" and "Document Title 6".

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# **i. Study Group Order**

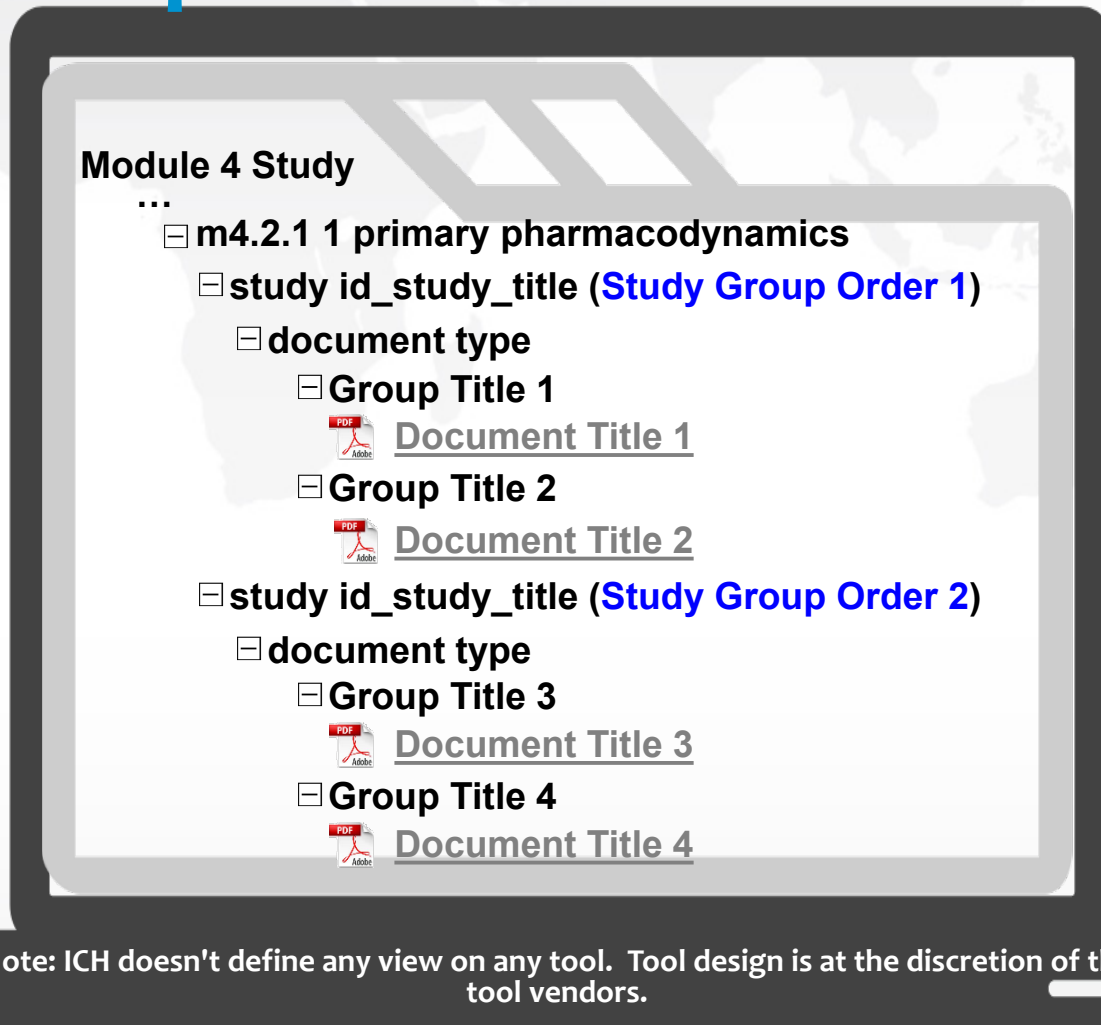
# Set order of Studies in a CTD section

- Uses Study Group Order Keyword with code values from 1 to 99
- Provides a mechanism to define the order that studies will be displayed in Modules 4 & 5
- The study group order keyword should only be used with the study id\_study title keyword
- Ability to order studies in a particular CTD section

# Apply Study Group Order

Possible views in the tool

- Senders can use the study group order keyword to add sequential ordering of study groups
- Applies to headings with a study identifier/study title keyword



The screenshot displays a hierarchical tree view within a tool interface. The root node is "Module 4 Study", followed by an ellipsis "...". Below this, there are two main study groups, each with a square expand/collapse icon to its left. The first group is "m4.2.1 1 primary pharmacodynamics", and the second is "study id\_study\_title (Study Group Order 2)". Each of these groups contains a "document type" sub-section, also with a square icon. Under "m4.2.1 1 primary pharmacodynamics", there are two "Group Title" entries: "Group Title 1" and "Group Title 2". Each group title is followed by a PDF icon and a "Document Title" entry: "Document Title 1" and "Document Title 2". Similarly, under "study id\_study\_title (Study Group Order 2)", there are two "Group Title" entries: "Group Title 3" and "Group Title 4", each followed by a PDF icon and a "Document Title" entry: "Document Title 3" and "Document Title 4". The "Study Group Order" keywords are highlighted in blue in the original image.

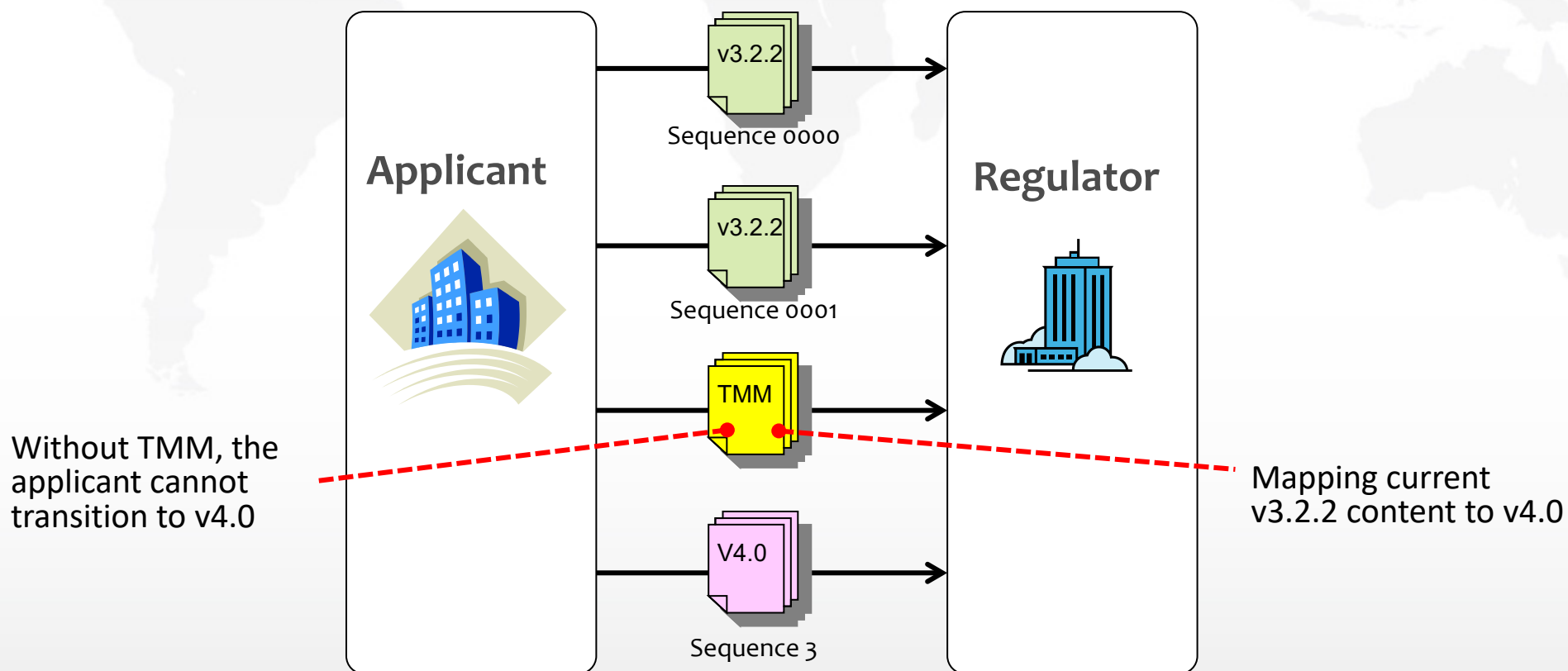
Note: ICH doesn't define any view on any tool. Tool design is at the discretion of the tool vendors.



## **3. Transition from v3.2.2 to v4.0**

# Transition Mapping Message

- What is Transition Mapping Message (TMM)?
  - The message submitted from the applicant to regulator when the application needs to transition from v3.2.2 to eCTD v4.0 format during its life cycle.

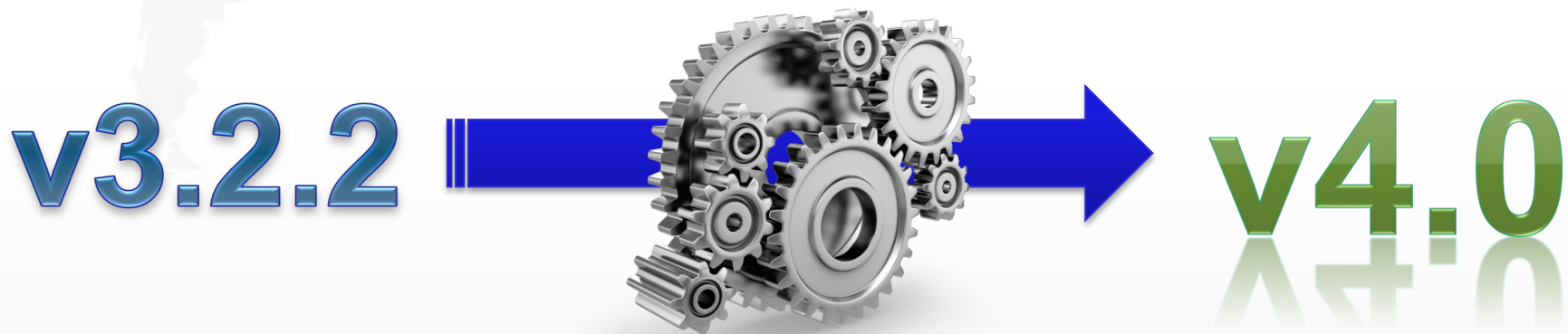


# How transition will work (high-level)

- Submit eCTD sequence- transition mapping message (TMM)
  - Current eCTD view will be transitioned.
    - Only submission content that has been submitted to the Regulatory Authority in eCTD format
    - All current submission contents should be transitioned regardless of whether or not the content will undergo life cycle.
      - Exclude deleted or replaced leafs
      - Includes append leafs
    - No changes included in transition message, make changes before or afterward but not in TMM.
    - No content files should be submitted for the transition mapping message

# Purpose of the transition message

- Enable Context of Use life cycle
- Enable reuse of documents
- Want to retire v3.2.2 in the future



## Considerations before transitioning to v.4.0

- Develop a strategy for managing sender-defined keywords.
  - Note this will allow for better utilization of grouped submissions when allowed in certain regions.
  - Recommend that keywords be managed across applications even though they need to be sent for each application.
  - Combine individual Study ID and Study Title keyword values.
- Ensure that the Transition Mapping Message is accepted by the Regulator before sending v4.0 message
- Only one valid TMM will be allowed – i.e., once the content is transitioned and the first v4.0 message is received, only v4.0 messages will be processed for that application.

## Tools needed to create and view v4.0 submissions

- Tools required to create/manage and view eCTD v4.0
- In comparison to eCTD v3.2.2,
  - No longer possible to manually create a pilot/sample submission.
  - Difficult to make manual corrections/fixes
  - Stylesheets will not be provided to view eCTD v4.0 content
- eCTD v4.0 submissions much more complex to create without tools



## 4. Region-specific Topics

## Region-specific Topics

- Grouped submissions – vary by region and may be:
  - A single Submission Unit with multiple Submission components
  - Multiple Submission Units included in one transmission (i.e., one Submission Unit for each Submission)
- Communication with regulators - The regulatory authority can send correspondence to the submitter via eCTD v4.0.
  - Applicants may receive and store sequences from regulatory authority along with applicant's submission contents.



## 5. Advantages of eCTD v.4.0

# Advantages of eCTD v4.0

- Harmonised submission unit:
  - All content from Module 1 through Module 5 is contained in one exchange message – i.e., an XML file covers both ICH and regional information.
- Document reuse:
  - Once a document has been submitted, the document may be reused by referencing its unique identifier (ID) from the same or different submission unit.
  - Allows reuse of meta-data (e.g., document title, language)
  - All the contents of the reused document, including references and hypertext links to other documents, should be relevant to the submission that reuses the document.
- Context of Use life cycle:
  - The Context of Use concept allows for advanced life cycle management operations. A Context of Use may be replaced by one or more Context of Use elements and vice versa (i.e., one to many, many to one) through the context of use life cycle.
  - eCTD v4.0 also introduces the ability to apply changes to keyword definition display name values (e.g., drug substance/product names, manufacturers, dosage forms, indication, excipient, group title, etc.) without resubmitting the physical files or the Context of Use element.

# Advantages of eCTD v4.0

- Function of context of use and keyword combinations:
  - The Context of Use and Keyword combination will function to create a group of documents.
  - One use of context groups includes the replacement for STFs in Modules 4 and 5 to organise multiple files relating to a single clinical study as noted in the eCTD specification v3.2.2.
- Controlled vocabularies (CVs):
  - Allowed values are captured in CVs providing for easier update without the need for system or tool updates
  - For sender-defined keyword values, previously submitted values can be corrected/replaced in subsequent submissions
- Additional document metadata
  - Document metadata may be used to identify submission content (e.g., datasets) that require additional processing