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Orientation Material
for
M8: eCTD EWG
eCTD v4.0 Implementation Package v1.6

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
June 2021	Updated based on the Implementation Package v1.4
May 2022	Updated based on the Implementation Package v1.5
May 2024	Updated based on Implementation Package v1.6 and CV Package 1.0

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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 concepts of v3.2.2 Forward Compatibility

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2. eCTD Concepts and Benefits

2.1 Key Messages

- With eCTD v4.0, you can
  - Reuse 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
  - Life cycle and reuse of v3.2.2 content.

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
j. Forward Compatibility

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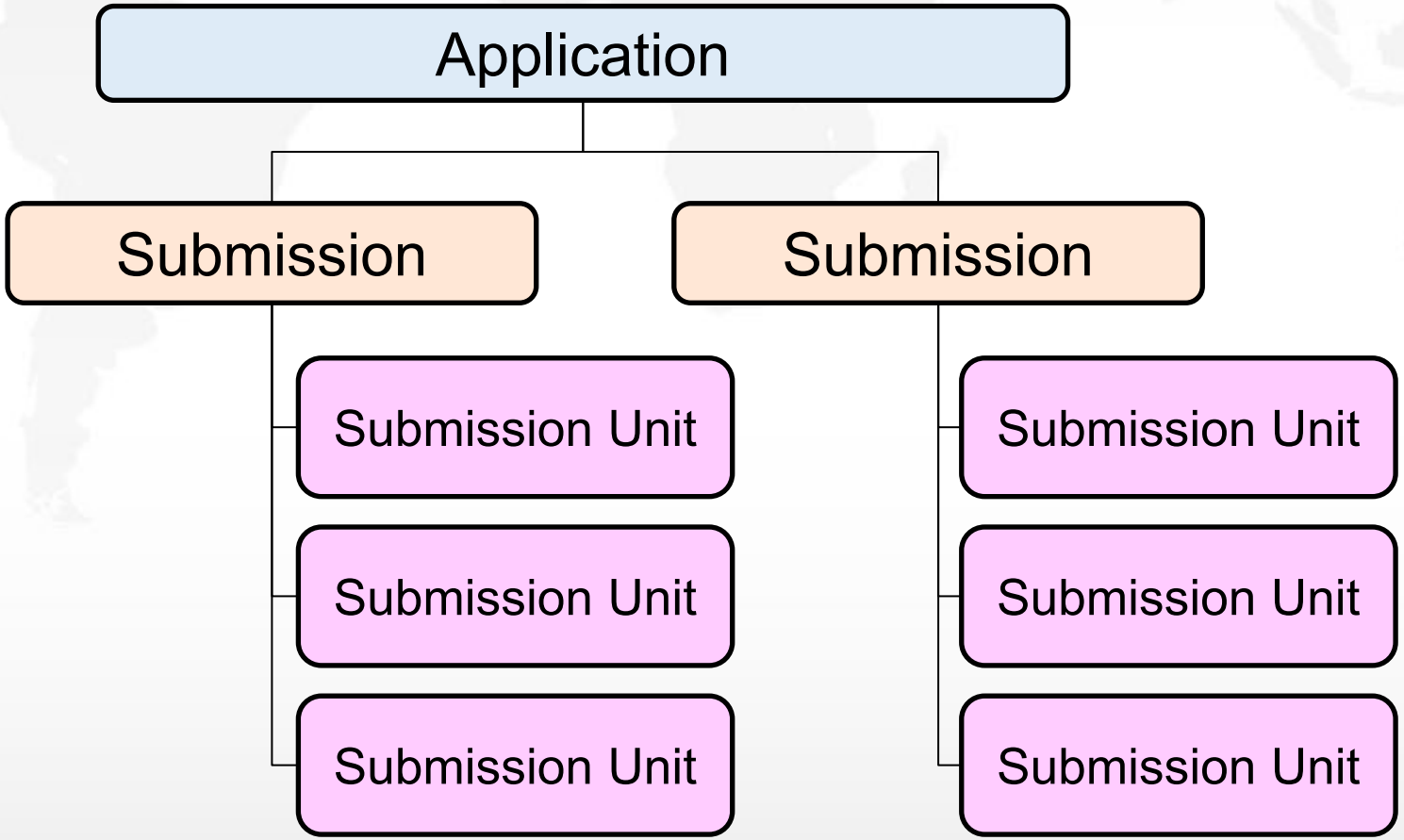
a. Application – Submission – Submission Unit

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.

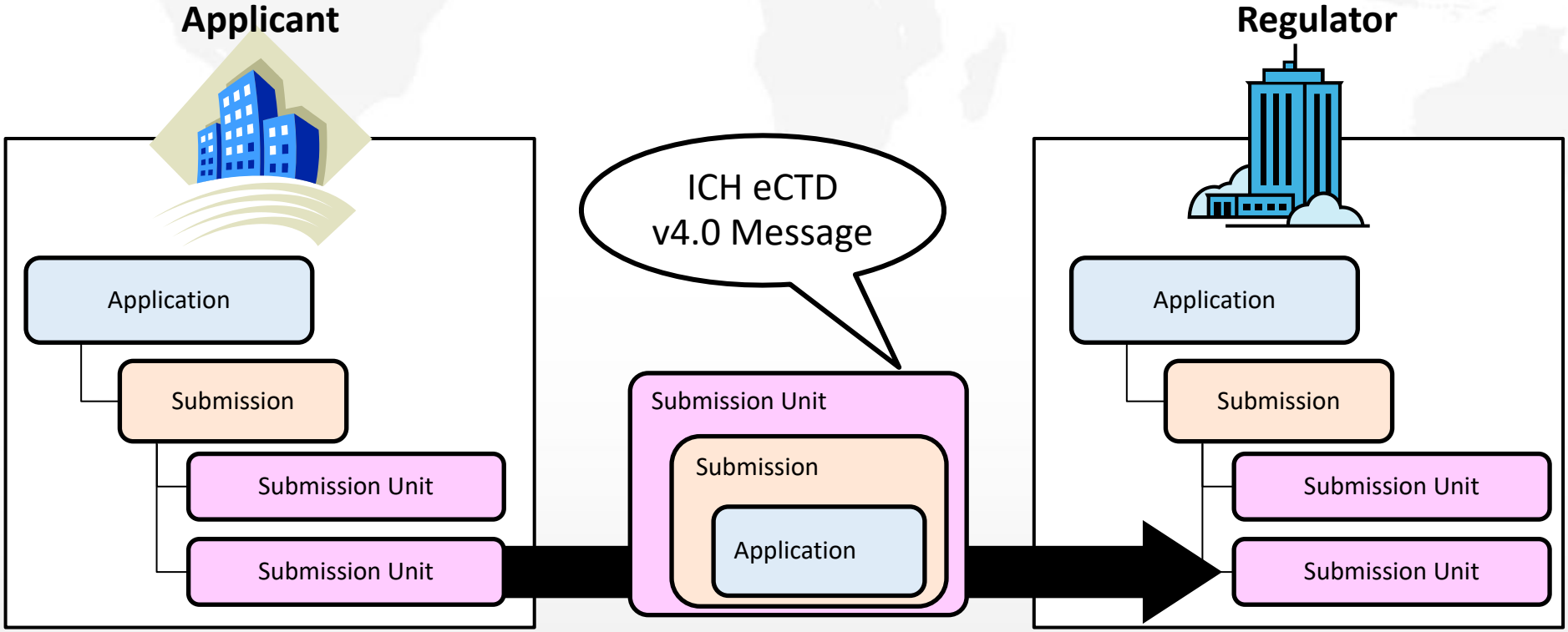
ICH eCTD v4.0 - Big Picture

- 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.

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b. Controlled Vocabulary

Consider adding the package decoupling

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 for each Code List version. Regions will specify the valid versions in their implementation.
- 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)

* See Regional CV list for values

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.

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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"*

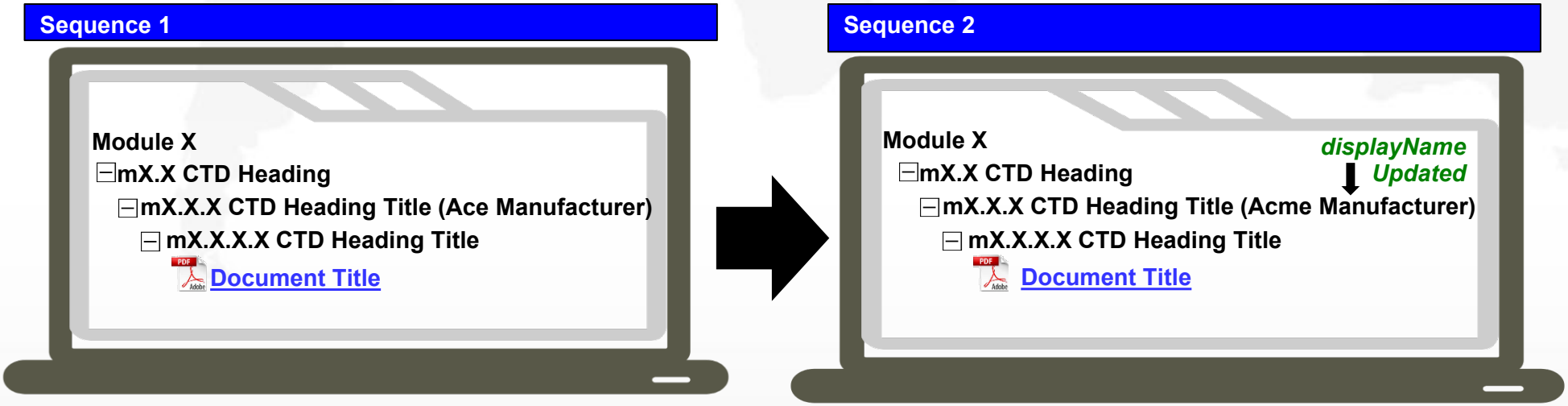
Develop a strategy for managing sender-defined keywords

- 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.
- Take into consideration use of v3.2.2 attributes (e.g., manufacturer) and values
- Combine individual Study ID and Study Title keyword values.

Update keywordDefinition displayName

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

Possible views on the tool



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

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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**)

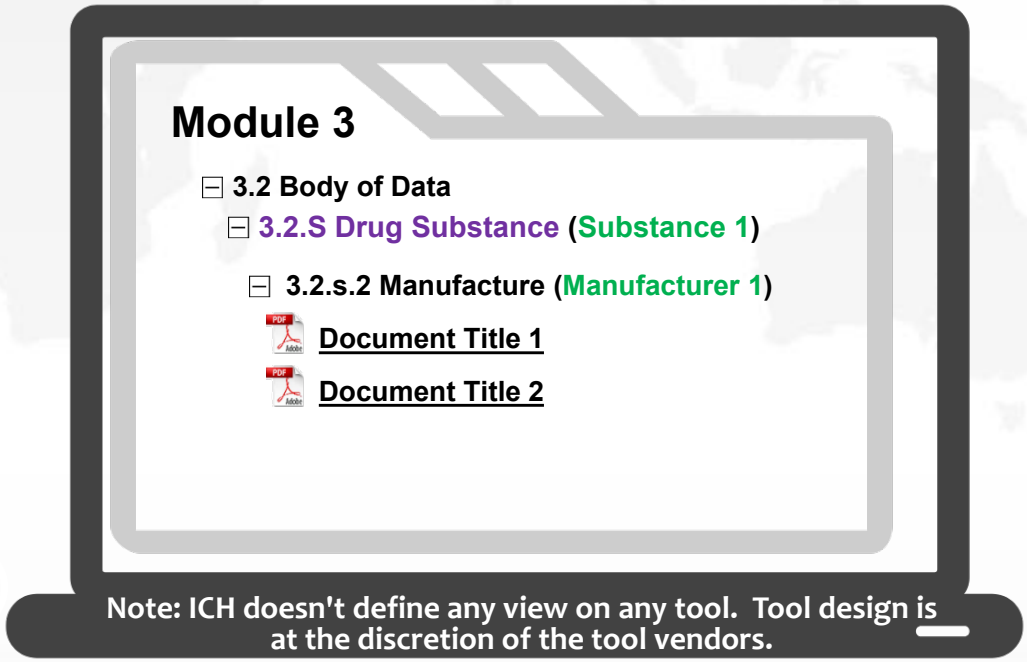
CoU and Keyword Combinations

- 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

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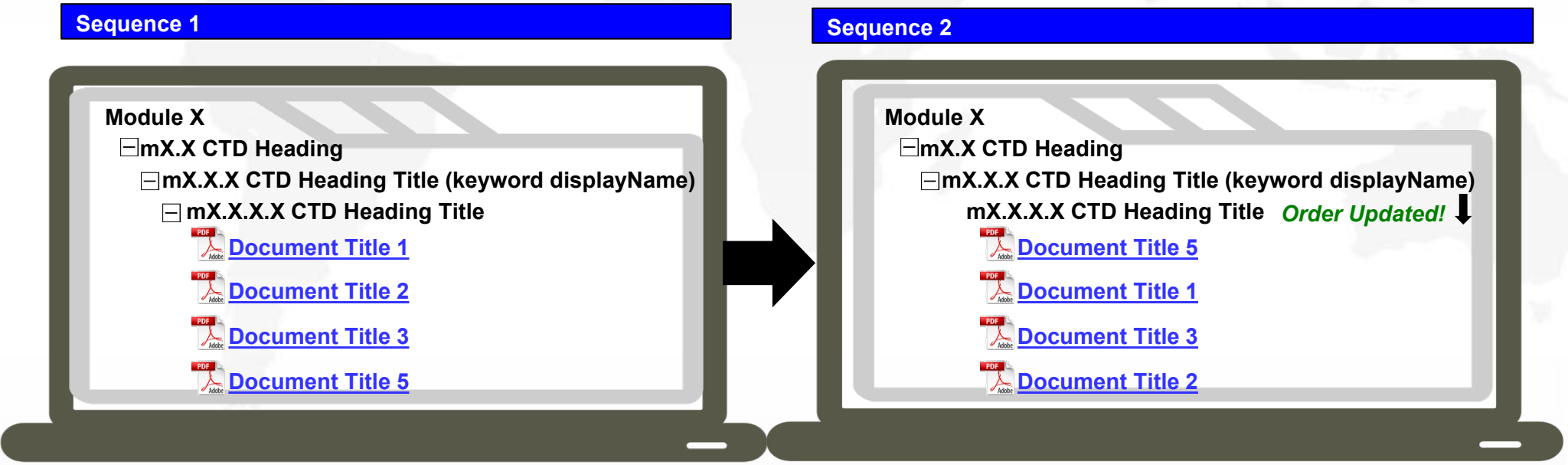
e. Ordering Content (Priority Number)

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



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f. Document Label

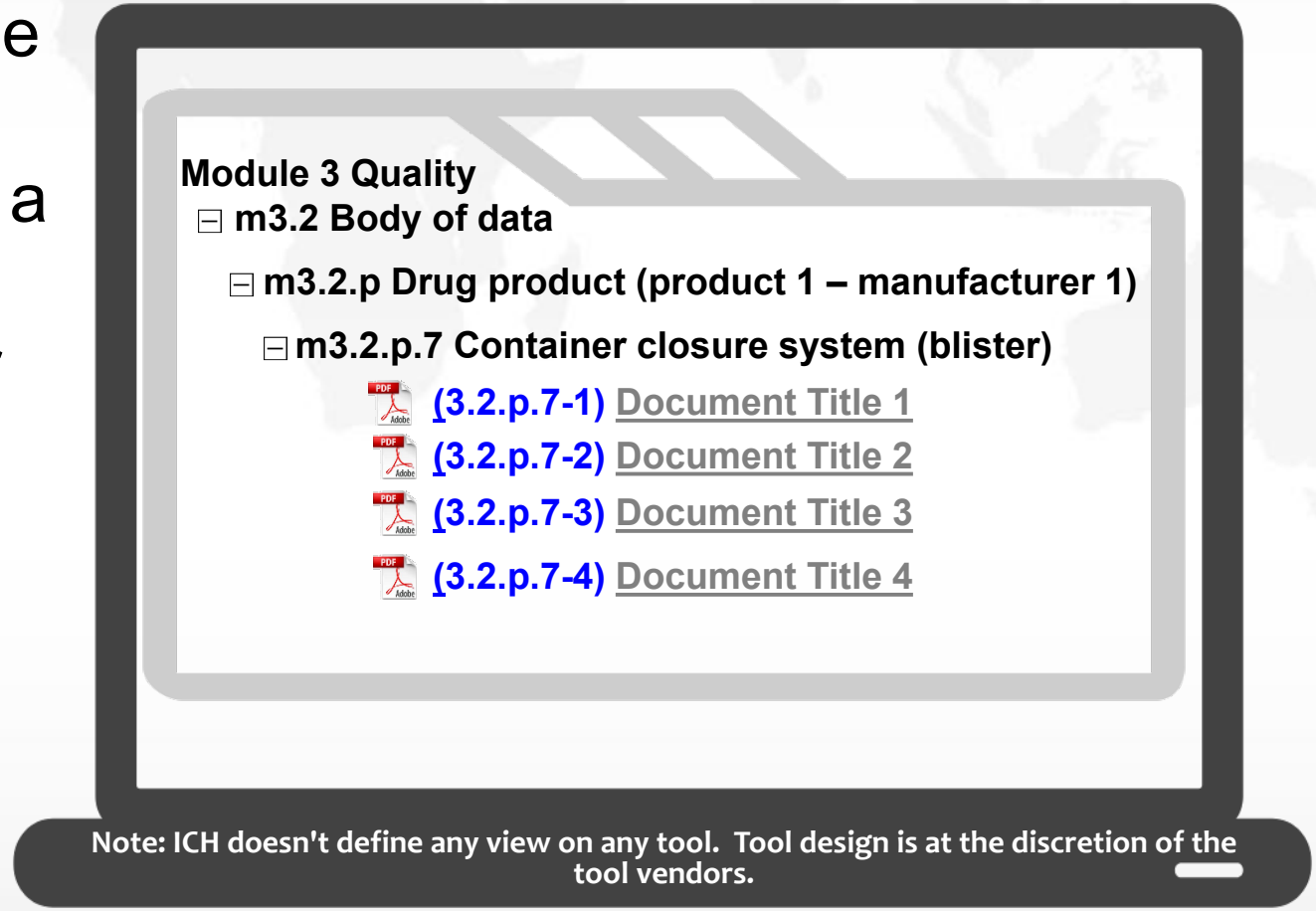
Document Label

- 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



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g. Documents

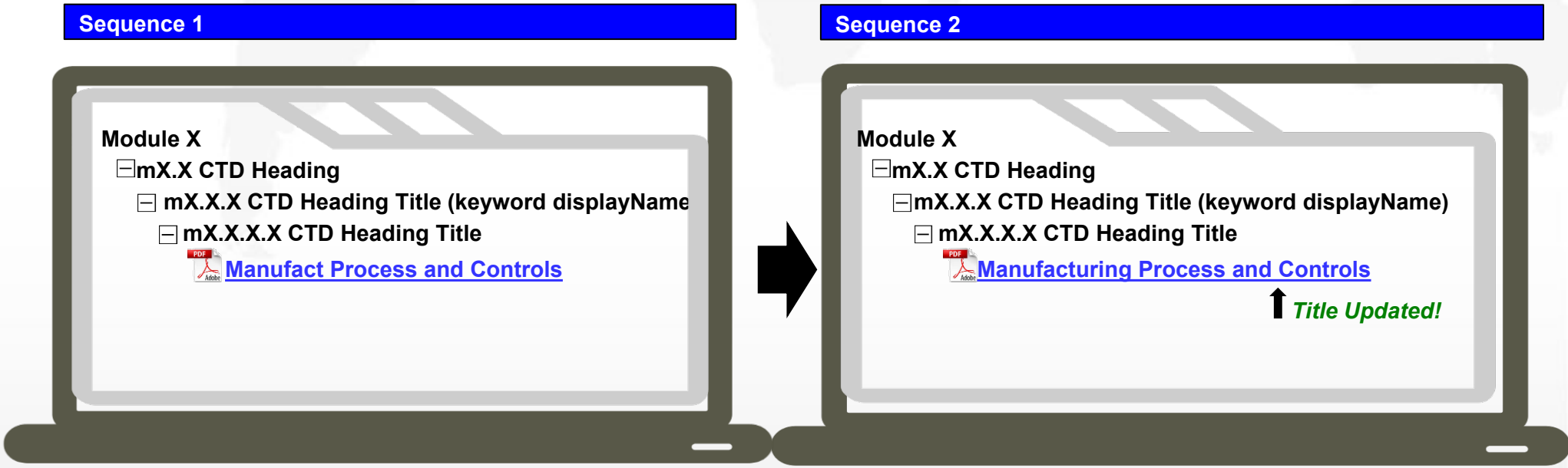
Reuse documents previously submitted

- 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



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h. Group Title

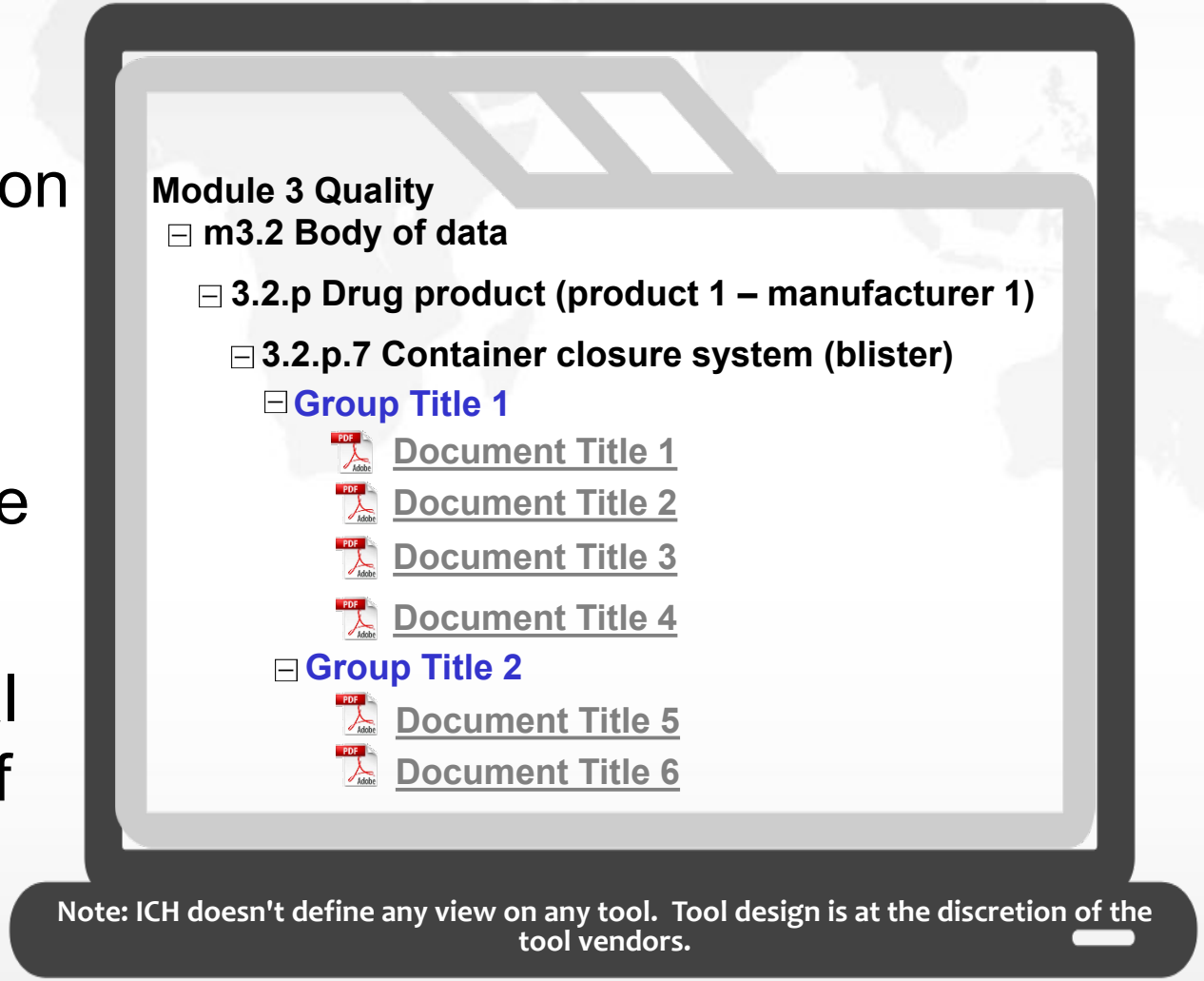
Grouping of content in a CTD section

- 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

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

Possible views in the tool



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i. Study Group Order

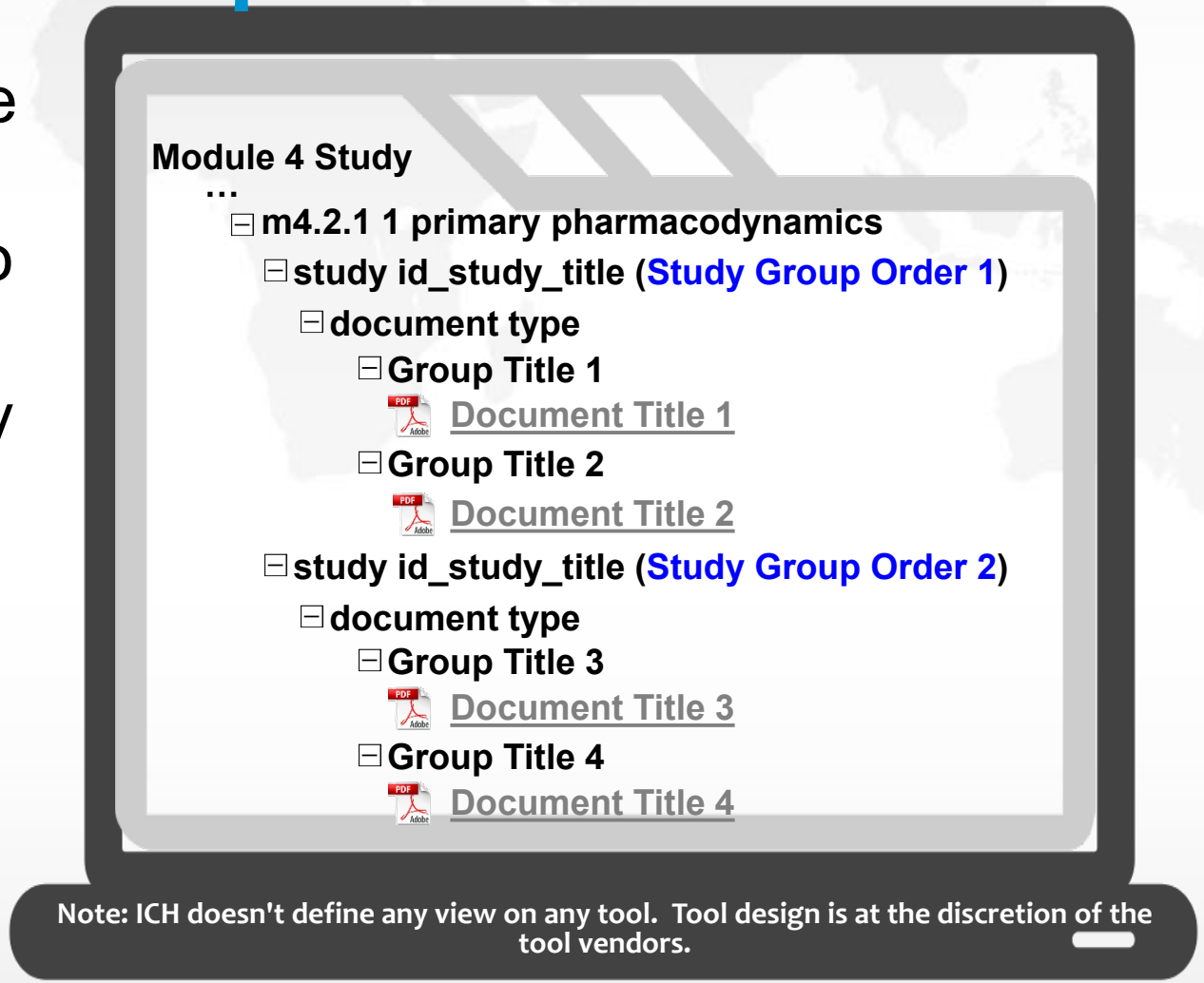
Set order of Studies in a CTD section

- 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

- 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

Possible views in the tool



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j. Forward Compatibility

Forward Compatibility

- Forward compatibility should be used for any dossier that has v3.2.2 content where the application is being converted to a v4.0 message. Integration of v3.2.2 content with v4.0 content shall enable:
  - Seamless presentation of v3.2.2 and v4.0 dossier content and information to users (i.e., builders/viewers/reviewers) with one tool to support publishing and viewing of complete dossier content comprising of v3.2.2 and v4.0 submissions.
  - Continuous reference to v3.2.2 content
    - Enabling life cycle of active v3.2.2 content
    - Enabling document reuse of v3.2.2 content, including applications that have not converted to v4.0
- Life cycle of submission content is only allowed for active (e.g., new, replace) leaf elements (i.e., content that is in the current view);
- When v3.2.2 content is replaced, it must follow v4.0 context group (i.e., CoU and keyword combination) life cycle rules;
- When submitting v4.0 content that should be grouped with v3.2.2 content the keyword codes and values must match.

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4. Region-specific Topics

Region-specific Topics

- Grouped submissions – vary by region
- 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.

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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