Support Documentation for

M8: eCTD EWG
eCTD v4.0 Implementation Package v1.3

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

Legal Notice

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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Note:
White box on top right corner of the following slides indicate corresponding section(s) on the eCTD v4.0 Implementation Package.

Introduction

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

Background

- The specification for the eCTD is based upon content defined within the CTD issued by the ICH M4 EWG.

- The structure and level of detail specified in the CTD was used to define the eCTD structure and content, but the CTD did not describe documents that can be submitted as amendments or variations to the initial application.

- The eCTD was defined as an interface for Regulated Industry to Regulatory Authority transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission.

- eCTD reached Step 4 in 2003, and with several minor updates, it was implemented in all the ICH regions. A major version (v4.0) was added by ICH M8 EWG and reached Step 4 in 2015.

- eCTD v4.0 is based on the HL7 RPS R2 Normative.

Purpose of eCTD v4.0 Documentation

- The ICH eCTD v4.0 Implementation Package (the Package) serves as the implementation guide and a technical specification for the eCTD v4.0 Modules 2 through 5 using the HL7 V3 RPS R2 Normative.

  o Implementers of v4.0 messages are the main audience of these documents.

  o Some files (e.g., schema and genericode files) are for use in systems – i.e., not human readable.
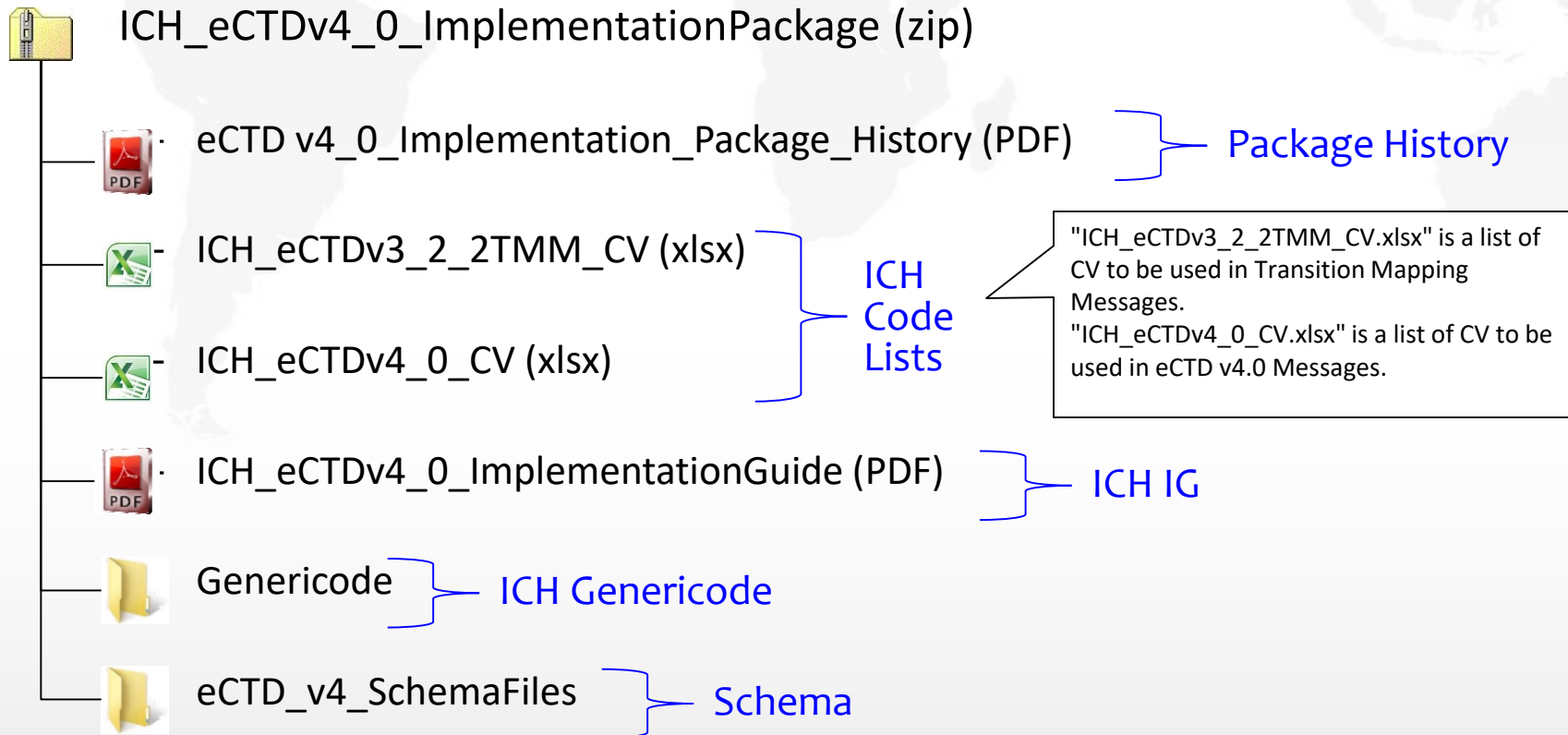
eCTD v4.0 Scope

- The scope of the ICH activities covers the human pharmaceutical product marketing approval processes.

- The Package covers the specification information for:
  - eCTD v4.0 Modules 2 - 5 submission contents, and
  - Transition message mapping from v3.2.2 to v4.0.

- The Package does NOT cover the specification information for:
  - The eCTD v4.0 Regional/Module 1 content, including the Regional Administrative and Product Information;
  - Transition message between other versions; or
  - How the tools should display eCTD v4.0 to the users.

- The Package defines the message for exchanging regulatory submission information electronically between Regulatory Authorities and the Pharmaceutical Industry.

- The eCTD v4.0 XML message provides the ability to describe the contents of the submission unit and all information needed to process an individual regulatory exchange between these two parties.
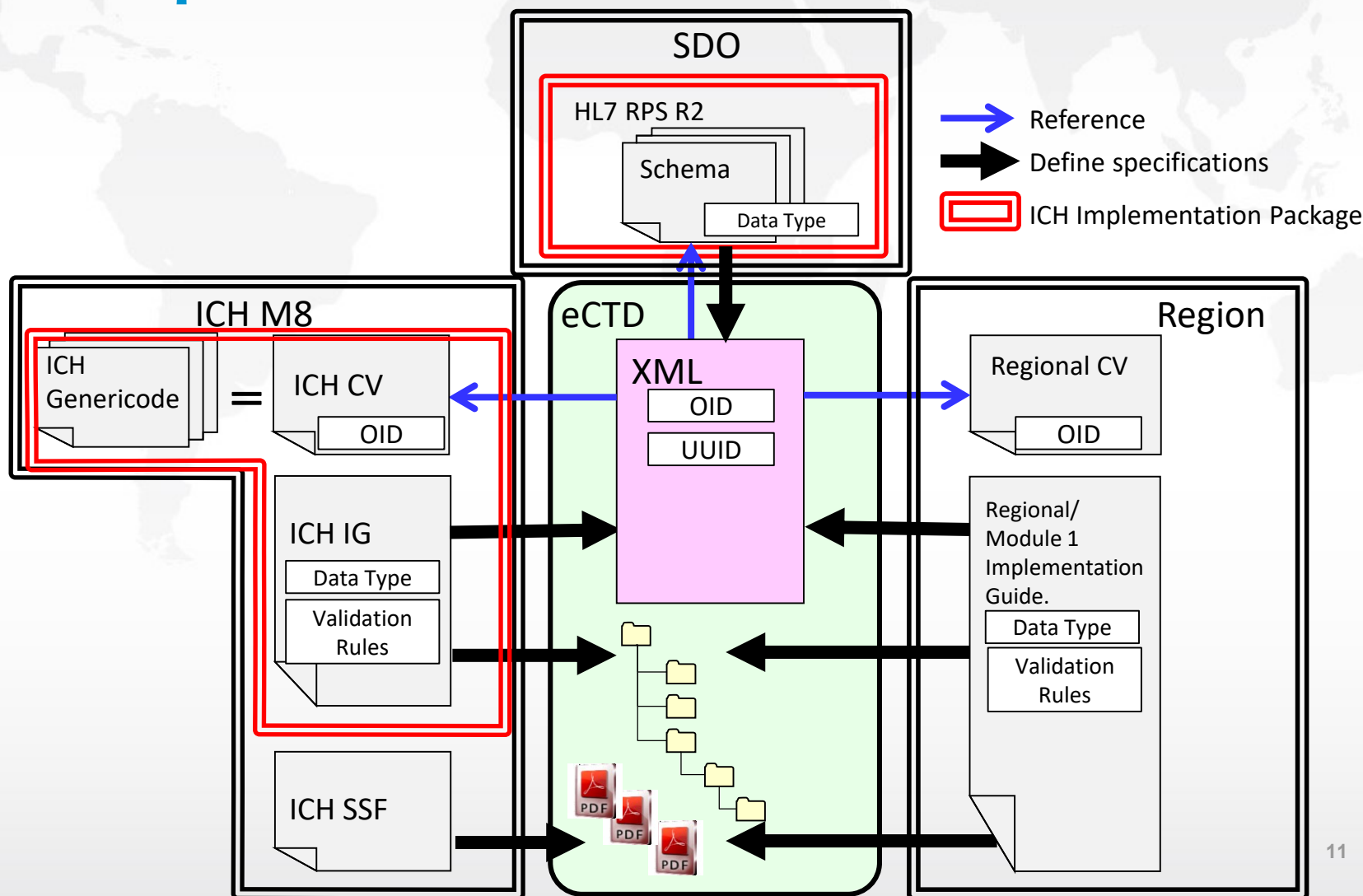
Advantages of eCTD v4.0

- Harmonised submission unit:
  - o 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:
  - o Once a document has been submitted, eCTD v4.0 will allow for the document to be reused by referencing its unique ID from the same or different submission unit.
  - o 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:
  - o 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., many to one) through the context of use life cycle.
  - o 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 Contexts of Use element.

- Function of context groups:
  - o The Context of Use code and Keyword code combination will function to create a group of documents in a specific context.
  - o 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.

eCTD v4.0 Support Documentation

eCTD v4.0 Implementation Package

- The following figure outlines the documents in the implementation package (zip file):

ICH_eCTDv4_0_ImplementationPackage (zip)

- eCTD v4_0_Implementation_Package_History (PDF) — Package History

ICH_eCTDv3_2_2TMM_CV (xlsx)

ICH_eCTDv4_0_CV (xlsx)

ICH Code Lists

"ICH_eCTDv3_2_2TMM_CV.xlsx" is a list of CV to be used in Transition Mapping Messages.
"ICH_eCTDv4_0_CV.xlsx" is a list of CV to be used in eCTD v4.0 Messages.

- ICH_eCTDv4_0_ImplementationGuide (PDF) — ICH IG

Genericode — ICH Genericode

eCTD_v4_SchemaFiles — Schema

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eCTD v4.0 Support Documentation

Components of the eCTD v4.0

eCTD v4.0 Support Documentation

eCTD v4.0 Components

| Components	Description
Schema	Defines the basic XML elements and attributes to be used in eCTD v4.0 XML messages. Since the schema was developed by HL7 and is not only for ICH eCTD v4.0, the users also needs to refer ICH IG for detailed instructions specific for ICH eCTD v4.0.
Data Type	Defines the type of value per element or attribute. Basic data types are defined by the HL7, but ICH IG or Regional Guidance could constrain them. Examples could be alpha, numeric, and etc.
ICH IG (Implementation Guide)	Technical specification for the eCTD v4.0 Modules 2 through 5 using the HL7 V3 RPS R2 Normative. eCTD v4.0 messages must follow this document.
ICH CV (Controlled Vocabularies)	Defines the valid values to be used for the information exchanged by the eCTD v4.0 XML Messages or Transition Mapping Messages.
ICH Genericode	Computer-readable format of the ICH CV.
Validation Rules	Defines the criteria which the eCTD v4.0 are validated against. The ICH IG contains the rules that all the ICH regions reject submission unit if it violates. Regional/Module 1 Implementation Guide could provide more detailed rules.
OID (Object Identifier)	Identifies the code lists on which the codes are defined. The code list could be owned by ICH, regional authority, or applicant.
UUID (Universally Unique Identifier)	Identifies the instances submitted by eCTD v4.0. For example, submission unit, submission, application, document, and etc. are all submitted with UUID.
ICH SSF (Specification for Submission Format)	Defines technical specification of the files exchanged by eCTD. The SSF is not only for v4.0, but it applies to all the versions of eCTD.
Regional/Module 1 Implementation Guide	Technical Specification for implementation of eCTD v4.0 in the region. It gives detailed instructions that apply to the region in addition to the ICH IG and SSF.
Regional CV	Defines the valid values to be used for the information exchanged by the eCTD v4.0 XML messages in the region.

Updating information

- Besides CoU life cycle, the eCTD v4.0 has the function that enables the sender to update the information previously submitted.

- The information that can be updated are:
  - Priority Number
  - Document title
  - Document mediaType
  - Document language
  - keywordDefinition displayName

- The update can affect beyond the sequence.

Information to update	Update affects	Remarks
Priority Number	Within the submission	This is to reorder the previously submitted CoUs.
Document title	Everywhere the document is referenced, even across the application	This is to correct an error (e.g., typo). If the concept needs to be changed, a new document should be provided.
Document mediaType		
Document language		
keywordDefinition displayName	Everywhere within the same application where the keywordDefinition is referenced	This is to correct an error (e.g., typo) or to update the display name without changing the concept. If the concept needs to be changed, a new keywordDefinition should be provided.

eCTD v4.0 Implementation Package Change Control

- Changes to the Implementation Package will be made as necessary, and may relate to any of the v4.0 components.

    - Minor changes will be considered those that may change the implementation rules and vocabulary, but not a change to the schema.

    - Major changes will be considered those that require changes to the schema files at the standards development stage, along with associated implementation rules and vocabulary changes.

- See next slide for Change Request information.
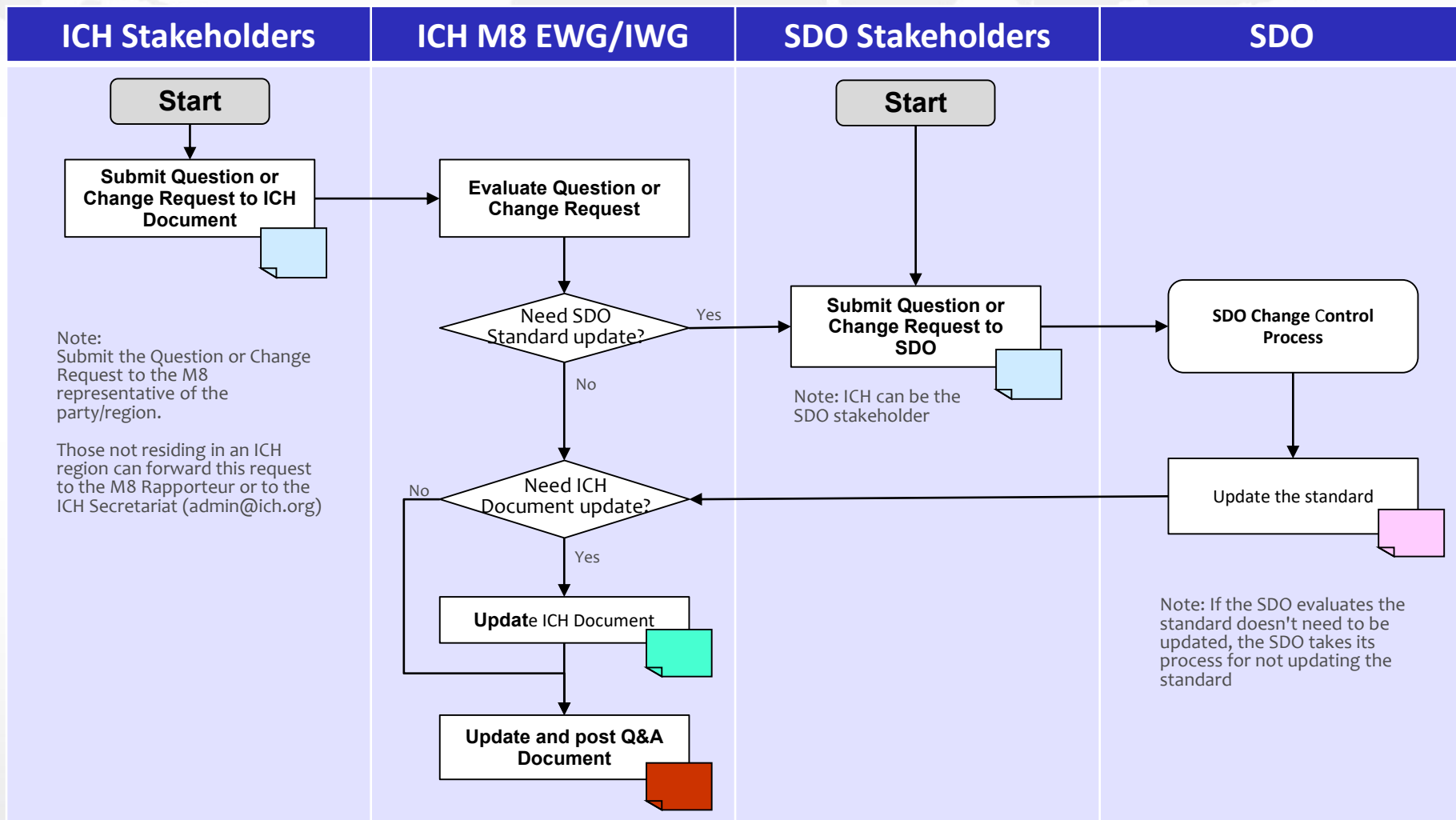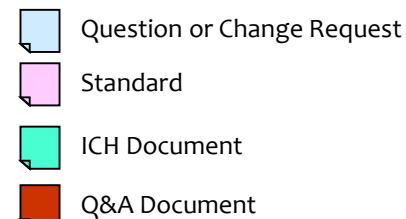
Regional/Module 1 Implementation Guides

- The Regional/Module 1 Implementation Guides play a key role in providing the administrative information.

- The administrative information in the message is mainly found in Module 1 and, as such, is the main subject of the Regional/Module 1 Implementation.

- Note to the Implementers
  - The information in this ICH eCTD v4.0 Implementation Guide is necessary, but not sufficient for creating the complete XML message for transmission. The Regional/Module 1 Implementation Guides are required to send a complete XML message.
  - The Regional/Module 1 Implementation Guides will be available through the ICH ESTRI website.

eCTD v4.0 Support Documentation

Excluded Business Processes

- The ICH documents will not address any regional business processes. The regional business process(es) may include, but are not limited to the following:
  - o Two-way Communication
    - includes information on Regulatory Authority communication with the Applicant.
  - o Dossier Management/Submission Life Cycle
    - includes rules for Submission Unit, Submission and Applications.
  - o Submission Units with Multiple Submission components (e.g., Grouped Submissions and Grouped Variations)
    - A single Submission Unit with multiple Submission components
    - Multiple Submission Units included in one transmission (i.e., one Submission Unit for each Submission).

- Refer to Regional/Module 1 Implementation Guides for additional information about Region/Country specific excluded business processes.

Basics of the eCTD v4.0 Submission Unit (including the XML Message and Submission Contents) and associated documentation

eCTD v4.0 Submission Unit

- **The eCTD v4.0 Submission Unit contains:**
  - submissionunit.xml
    - One eCTD v4.0 Message includes both content from Regional/Module 1 and Module 2 – 5.
    - Refer to Section 5.1.
  - sha256.txt
    - Checksum for the submissionunit.xml file
    - Replaces md5.txt files
    - Refer to Section 5.1
  - Folders and Files
    - Contain the folder structure and files for the contents included in the XML message.
    - Refer to Sections 4.1, 5 and 11 (Appendix 1).

ICH eCTD v4.0 Submission Unit – Big Picture of Message

- ## Applicant submits Submission Units to Regulator.
    - o A Submission Unit has the information about the Submission and Application to which it belongs.
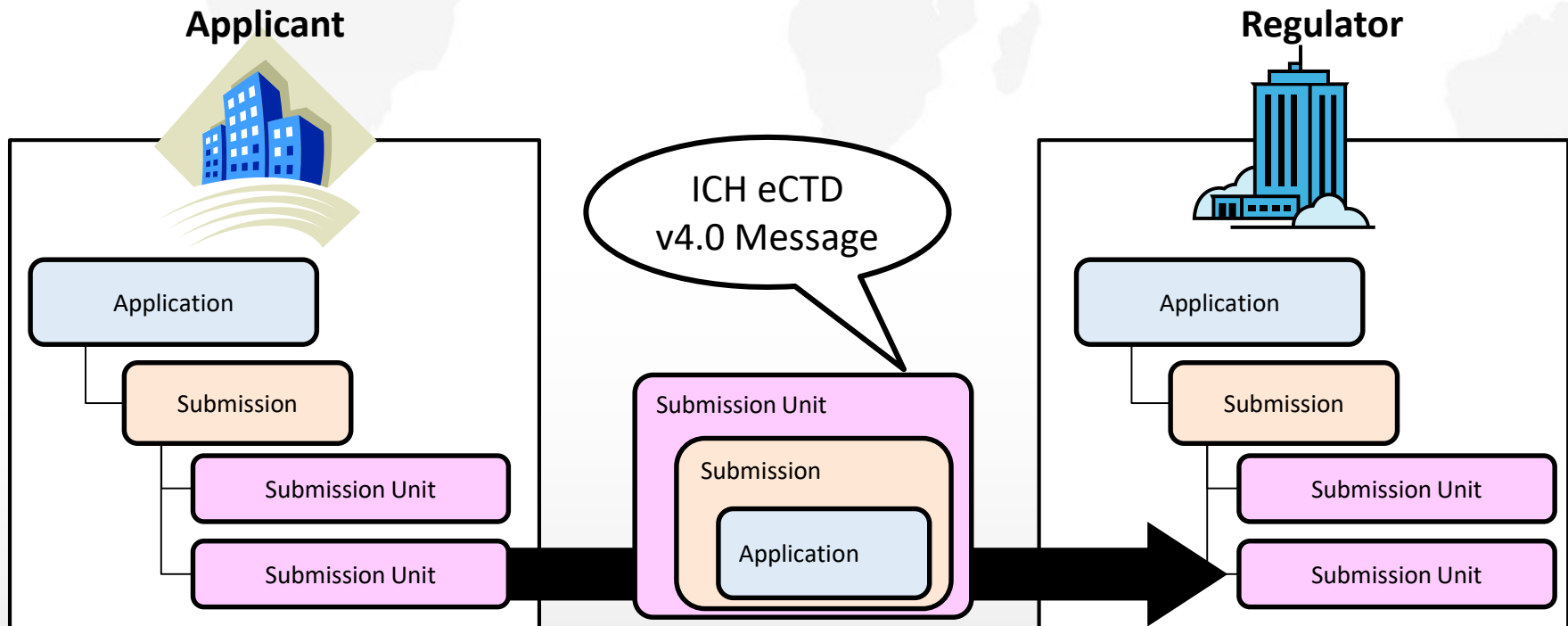
Note: Two-way communication is excluded from ICH business cases.

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ICH eCTD v4.0 Hierarchical Structure

- **3-layered hierarchy - A Submission Unit belongs to a Submission, and a Submission belongs to an Application.**
  - o Submission Unit
    - Also known as sequence
      - Includes the assignment of a sequence number.
    - Applicants submit a Submission Unit to regulator.
    - Could belong to multiple Submissions (e.g., Grouped submissions in some regions).
  - o Submission
    - Holds one or many Submission Units.
    - Each region defines the rules for this element.
  - o Application
    - Holds one or many Submissions.
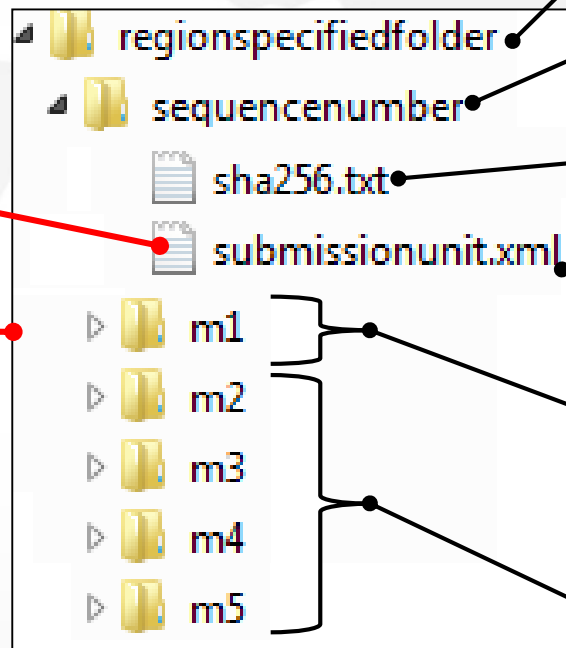   - Each region defines the rules for this element.

eCTD v4.0 Support Documentation

Submission Contents, Folder and File Structure

eCTD

XML
OID
UUID

regionspecifiedfolder
sequencenumber
sha256.txt
submissionunit.xml
m1
m2
m3
m4
m5

Folder name is determined by the region.

Folder name is the sequence number (e.g., "1", "2", etc.).

File name should be "sha256.txt".
SHA-256 checksum value is given as the body of text file.

File name should be "submissionunit.xml".
Refer to the ICH IG and Regional/Module 1 Implementation Guide.

Structure of m1 folder should follow Regional/Module 1 Implementation Guide.

Structure of m2-m5 folders should follow ICH IG. All files included in these folders should be accounted for in the XML message.
Files previously sent do not need to be sent again.

No schema file should be submitted.

eCTD v4.0 XML Message Basics - Identifiers

- **2 types of identifiers**
  - o Object Identifier (OID)
    - Identifies the code lists on which the codes are defined.
      The code list could be owned by ICH, regional authority, or applicant.
    - Given as a value for codeSystem attribute of code element.
    - Human-readable for those who understand the numbers.
    - Example: `<code code="ich_2.5" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>`

      ```
      ICH =     2.16.840.1.113883.3.989
      M8 Step 4 =   2.16.840.1.113883.3.989.2.2.1
      CoU =     2.16.840.1.113883.3.989.2.2.1.1.1
      ```

  - o Universally Unique Identifier (UUID)
    - Uniquely identifies the instance.
    - Given as a value for root attribute of id element.
    - Universally Unique Identifier (8-4-4-4-12 characters; each number is hexadecimal).
    - Not human readable.
    - Example: `<id root="550e8400-e29b-41d4-a716-446655440000"/>`

- **Other Identifiers may be regionally defined.**
  - o E.g., ID extension

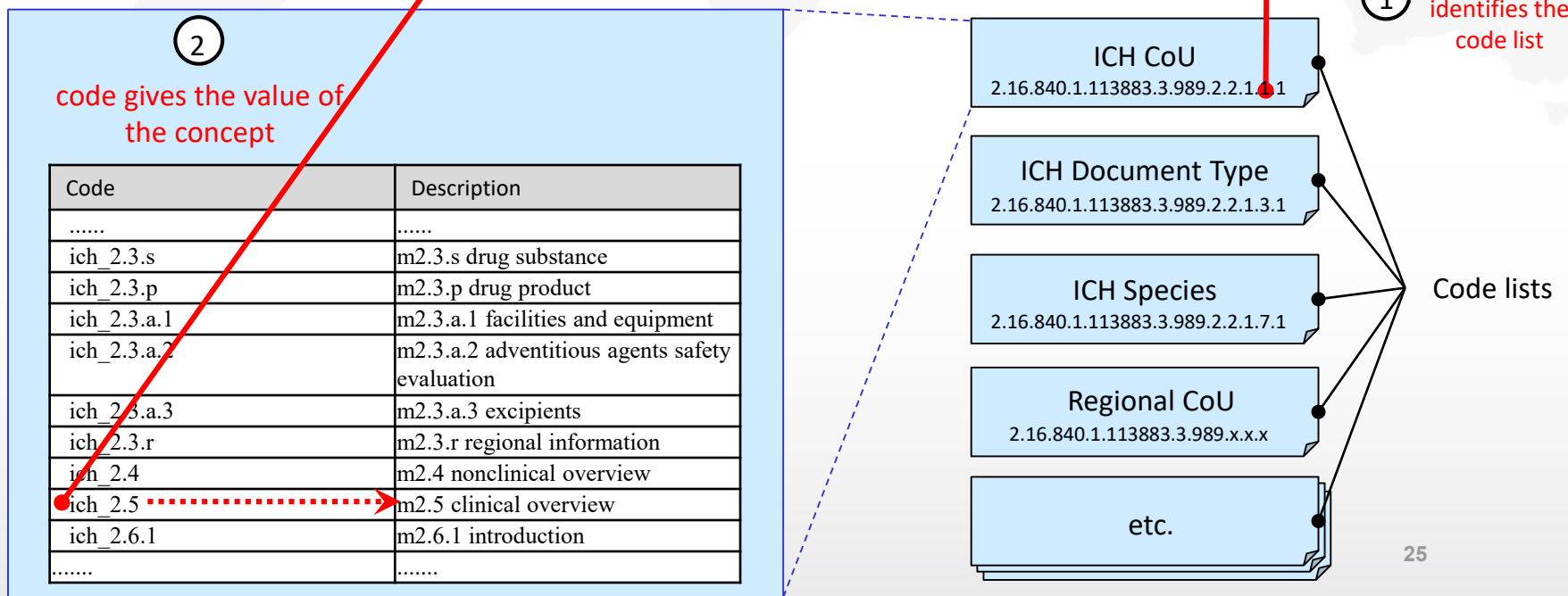# eCTD v4.0 XML Message Basics – Controlled Vocabularies

- **Controlled Vocabularies (CV) enable interoperability.**
  - Clear, unambiguous communications between systems sending and receiving XML messages.
  - For the XML elements that have coded values, a controlled vocabulary will be required to indicate the value of the concept.
  - Each code has a code system. The code system may be managed by ICH, Region or the Applicant. The specific assignment of code system values can be found in the detailed description of OIDs and controlled vocabularies.

- **Controlled vocabularies are defined external to the message.**
  - A code is used as the identifier to convert the code value into the meaningful terms that will be used in any system that implements the viewing of the information sent in the XML message.

- **5 types of Controlled Vocabularies**
  - Specified by ICH
  - Specified Regionally
  - Specified by HL7
  - Specified by External Organization
  - Sender-defined CV

- **Controlled vocabulary is provided in the Code List spreadsheet and genericode files (see zip file).**

eCTD v4.0 XML Message Basics - Codes

- **v4.0 essential elements have code and code system attributes.**
  - o Code system indicates which code list the code references.
  - o Code gives the value of the concept.
  - o Example:
    `<code code="ich_2.5" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>`

② code gives the value of the concept

Code	Description
......	......
ich_2.3.s	m2.3.s drug substance
ich_2.3.p	m2.3.p drug product
ich_2.3.a.1	m2.3.a.1 facilities and equipment
ich_2.3.a.2	m2.3.a.2 adventitious agents safety evaluation
ich_2.3.a.3	m2.3.a.3 excipients
ich_2.3.r	m2.3.r regional information
ich_2.4	m2.4 nonclinical overview
ich_2.5	m2.5 clinical overview
ich_2.6.1	m2.6.1 introduction
....	....

① codeSystem identifies the code list

ICH CoU
2.16.840.1.113883.3.989.2.2.1.1.1

ICH Document Type
2.16.840.1.113883.3.989.2.2.1.3.1

ICH Species
2.16.840.1.113883.3.989.2.2.1.7.1

Regional CoU
2.16.840.1.113883.3.989.x.x.x

etc.

Code lists

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eCTD v4.0 XML Message Overview – Message Header

- **Message Header comes before the payload.**

eCTD v4.0 Message

Message Header

Control Act Process

Submission Unit   1..1

Submission   1..*

Application   1..*

XML Declaration
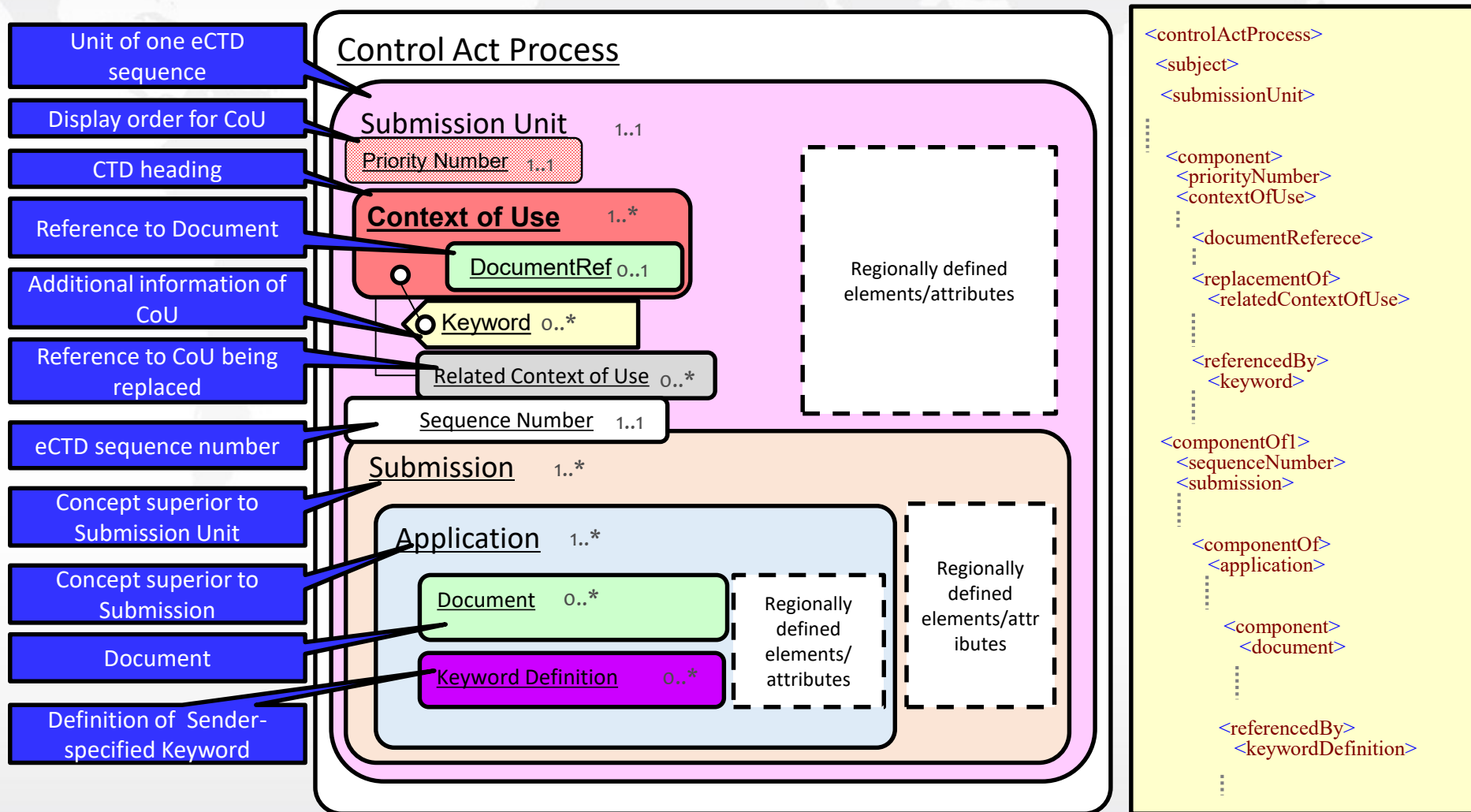
```
<?xml version="1.0" encoding="UTF-8"?>
<PORP_IN000001UV ITSVersion="XML_1.0" xmlns="urn:hl7-org:v3"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xsi:schemaLocation="urn:hl7-
org:v3 PORP_IN000001UV.xsd">
  <id/>
  <creationTime/>
  <interactionId/>
  <processingCode/>
  <processingModeCode/>
  <acceptAckCode/>
  <receiver>
    <device classCode="DEV" determinerCode="INSTANCE">
      <id>
        <item root="" identifierName=""/>
      </id>
    </device>
  </receiver>
  <sender>
    <device classCode="DEV" determinerCode="INSTANCE">
      <id/>
    </device>
  </sender>
  <controlActProcess classCode="ACTN" moodCode="EVN">
    <subject typeCode="SUBJ" >
      <submissionUnit>
        :
```

Message Header

Payload starts from here.

eCTD v4.0 XML Message Overview - Payload

eCTD v4.0 XML Message Basics – Submission Unit, Submission, Application

- The submission tracking information is specified by the Regional/Module 1 Implementation Guides.
  - o Rules and Controlled vocabulary is defined by Regions for submission unit, submission and application.
  - o One submission unit per message is expected.

eCTD v4.0 Support Documentation

eCTD v4.0 XML Message Basics - Context of Use

- What is "Context of Use"?
  - o It gives a context to the document it references.
  - o In eCTD, the context is the CTD heading.

> 2.3.S   DRUG SUBSTANCE (NAME, MANUFACTURER)

  - o Without being referenced by a CoU, a document is not assigned to any CTD heading.
  - o Keyword gives additional information to the CoU it is assigned (e.g., manufacturer).
  - o Combination of CoU code, codeSystem, and keyword(s) define the context.
    - If any one of them is different, the context is considered different.
  - o CoU status is "active" when it is relevant, "suspended" when it is removed, or "obsolete" when it is replaced. Note that "obsolete" is not used in the XML message because the system will change the status in its database when the CoU is replaced (i.e., when relatedContextOfUse is present).

Context of Use
ID Root = UUID
Code = Code for the CTD Heading
Code System = OID
Status Code = Active (or Suspended)

Keyword.code
Additional Information of this CoU

DocumentReference.id = UUID
Links document to the context of its use

RelatedContextOfUse.id = UUID
Indicates content that is being replaced

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eCTD v4.0 XML Message Basics – Life Cycle

- Basics
  - Life cycle operation occurs only at Context of Use.
    - When a sender intends to replace/remove document previously submitted, the technical operation is to replace/remove the CoU which references the intended document.
  - Document doesn't have a status, and thus life cycle doesn't occur at the document level.
    - Document is relevant to the review when referenced by active CoU.
    - All Documents must be referenced by a CoU
  - CoU is removed when it is submitted with statusCode "suspended".
  - CoU is replaced when new CoU is submitted with Related Context of Use.

Context of Use
ID = UUID •————————————— UUID of the replacing CoU
...

Related Context of Use
ID = UUID •————————————— UUID of the CoU being replaced

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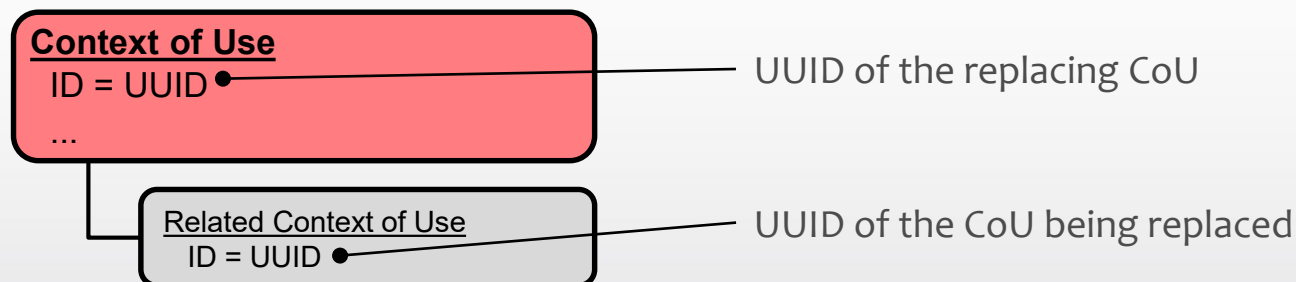
Removing / Suspending Context of Use Elements (Life Cycle)

- If the CoU needs to be removed at any time during the life cycle of the submission, a submission unit may indicate the removal of the CoU by changing the statusCode element.
  - From "active" to "suspended".
  - Only the <priorityNumber>, <id>, and <stausCode> elements are needed.
  - Submission of the other information (e.g., document reference, keywords) can be omitted.
  - ID must be the same to identify the CoU to be removed.
  - priorityNumber should be the same. Even if different value is provided, it will not be processed (i.e., the new priorityNumber would not be applied).
  - Once suspended, the same CoU (i.e., the same ID) cannot be reactivated.

Replacing (Versioning) Context of Use Elements

- 2 reasons for submitting a replacement:
  - The submission contents (i.e., the document being referenced) have changed.
  - The previous suspended submission content needs to be resubmitted.

- CoU Replacement can only occur between the same combination* of CoU code and keyword code.
  - If any one of them is different, CoU replacement is not allowed.

- Once being replaced;
  - The status is automatically changed to "obsolete" by the system, and the CoU cannot be reactivated.
  - The priority number is released, so the replacing CoU can have the same or different priority number.

- Replacement can occur between:
  - One CoU and one CoU
  - One CoU and many CoUs
  - Many CoUs and one CoU
  - Many CoUs and many CoUs

*The combination includes both the code and code system for the Context of Use and Keyword in order to define the specific context group under which the documents are grouped.

eCTD v4.0 Support Documentation

Replacing (Versioning) Context of Use Elements (cont'd)

- If you want to change the combination by CoU replacement,
  - o It is not allowed.
  - o No means to add, remove, or change any of those by CoU replacement.
  - o Suspend the CoU, and submit a new CoU (i.e., new CoU id) with edited information.
    - Reference the same document id if not intending to change the document.

- What if the M4 Annex: Granularity Document is updated and there are changes to the allowed granularities?
  - o Still, changing the combination by CoU replacement is not allowed.
  - o Suspend the CoU, and submit a new CoU (i.e., new CoU id) with edited information.

Updating information

- Besides CoU life cycle, the eCTD v4.0 has the function that enables the sender to update the information previously submitted.

- The information that can be updated are:
  - Priority Number
  - Document title
  - Document mediaType
  - Document language
  - keywordDefinition displayName

- The update can affect beyond the sequence.

Information to update	Update affects	Remarks
Priority Number	Within the submission	This is to reorder the previously submitted CoUs.
Document title	Everywhere the document is referenced, even across the application	This is to correct an error (e.g., typo). If the concept needs to be changed, a new document should be provided.
Document mediaType		
Document language		
keywordDefinition displayName	Everywhere within the same application where the keywordDefinition is referenced	This is to correct an error (e.g., typo) or to update the display name without changing the concept. If the concept needs to be changed, a new keywordDefinition should be provided.

Transition Mapping Message

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.

Applicant

Regulator

v3.2.2
Sequence 0000

v3.2.2
Sequence 0001

TMM

V4.0
Sequence 3
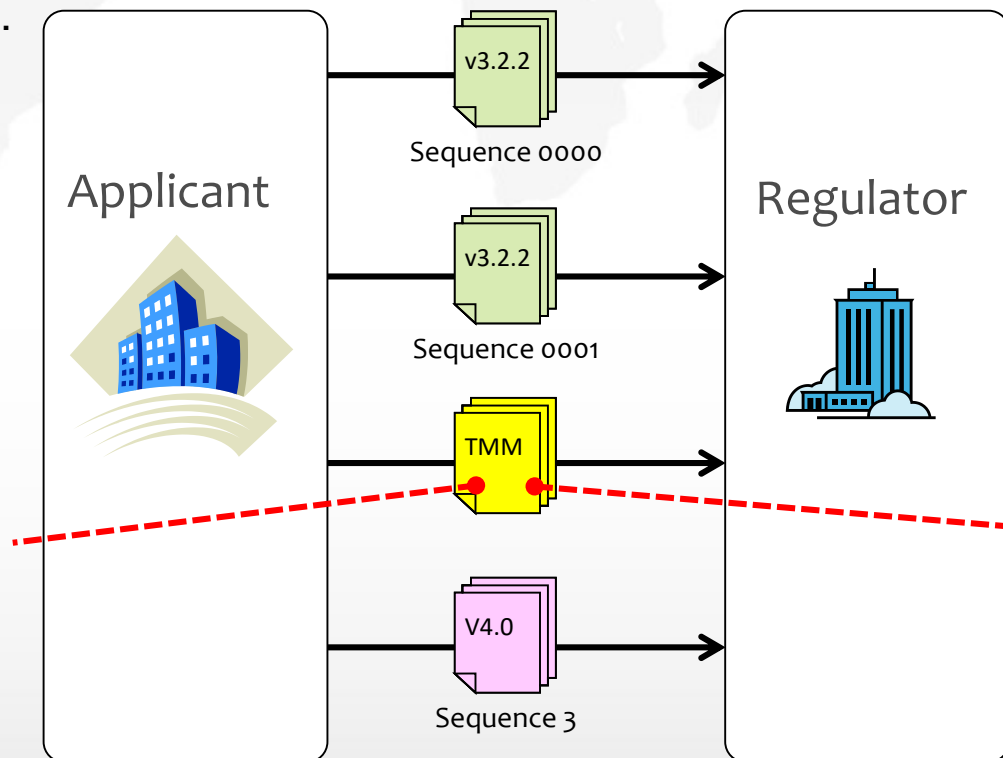
Without TMM, the applicant cannot transition to v4.0

Mapping current v3.2.2 content to v4.0

ICH IG section reference:
10.1 Overview of the Transition Mapping
Message

Transition Mapping Message (cont'd)

- What should be transitioned to v4.0 by submitting TMM?
  - o Only submission content that has been submitted to the Regulatory Authority should be included in the transition mapping message.
  - o All current submission contents should be transitioned regardless of whether or not the content will undergo life cycle.
    - Excludes any leaf elements that were deleted or replaced.
    - Includes leaf elements that have append status and its associated leaf.
  - o No change to the CTD heading is allowed in transition mapping message.
  - o Only two files should be submitted for the transition mapping message - i.e., the submissionunit.xml and sha256.txt files.
    - File should not be resubmitted.

eCTD v4.0 Support Documentation

Transition Mapping Message (cont'd)

- Transition Mapping Message Process
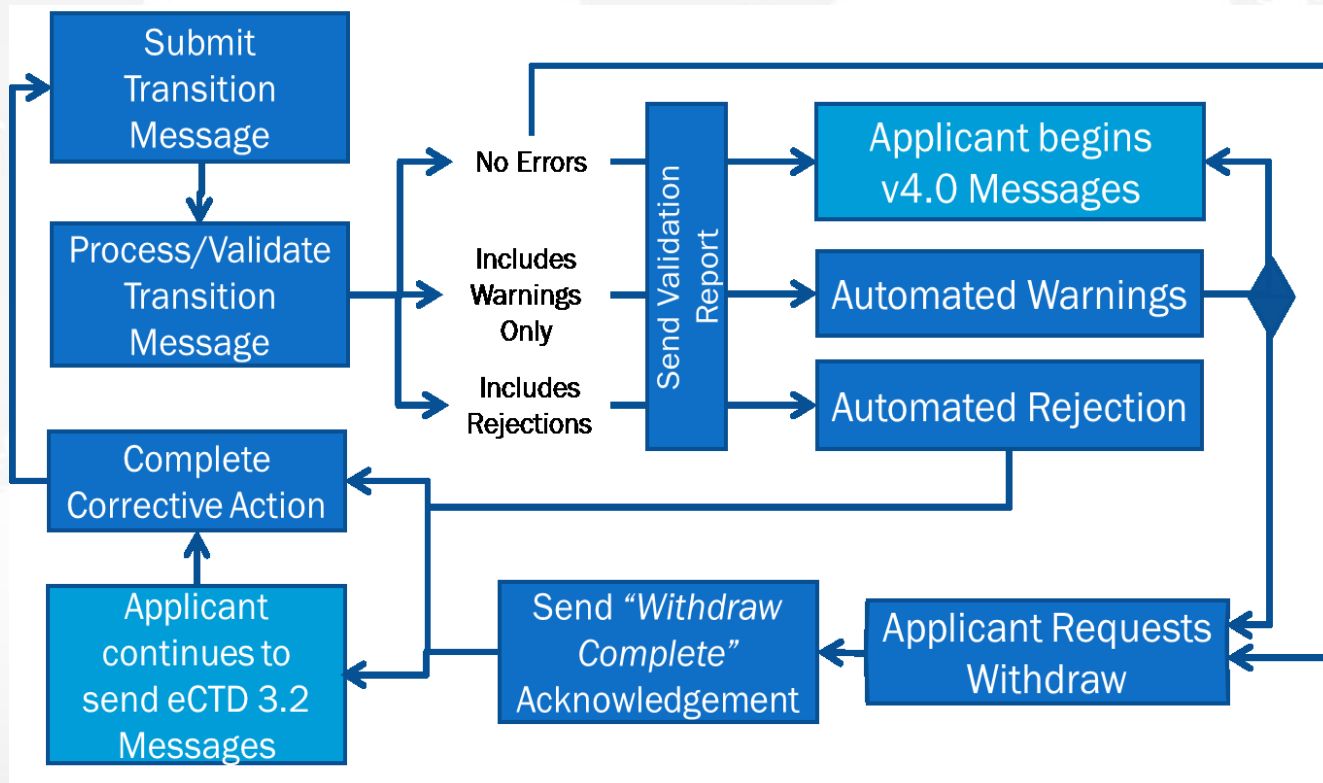
Transition Mapping Message (cont'd)

- The v4.0 schemas are used for the TMM.

- Instructions for TMM are located in Section10 and 13 of the eCTD v4.0 Implementation Guide.

- Not all v4.0 elements and attributes are used in the TMM.

- Different rules apply to some elements and attributes. – e.g., Submission code is set for the TMM; no life cycle is allowed; no changes to current view are allowed.

- 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.

ICH IG section reference:
12. Appendix 2: Validation of
The eCTD v4.0 message

13. APPENDIX 3: Transition mapping
message validation rules

ICH Validation Rules

ICH Validation Rules

- The Appendix 2 and 3 of the Implementation Guide gives the lists of ICH-harmonized validation rules applied to the eCTD v4.0 messages and TMM, respectively.
  - o If the message is invalid against the ICH Validation Rules, it would be rejected in all the ICH regions.
  - o If the message is valid against the ICH Validation Rules, there still are Regional Validation Rules that the message has to be compliant with.
    - If it is invalid against Regional Validation Rules, it could be rejected in that region.
    - Refer to Regional Guidance for regional validation rules.

Specification for Submission Format

- This submission format specification is additional guidance regarding the submission contents and is separate from the actual eCTD v4.0 Implementation Package

- Guidance is related to File format specification – e.g., PDF pagination, fonts, file size limits and security

Questions,
Change Requests

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

Question or Change Request?

- Submit an "eCTD Q&A or Change Request" to the M8 member of your party/region.

  o "eCTD Q&A or Change Request" form is found at eCTD v4.0 page on http://www.ich.org/products/electronic-standards.html

- Those not residing in an ICH region can forward it to the M8 Rapporteur or to the ICH Secretariat (admin@ich.org)