Orientation Material for

M8: eCTD EWG
eCTD v4.0 Implementation Package v1.2
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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
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• Benefits of eCTD v4.0
• Transition to eCTD v4.0
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Objective of this presentation

• Target audience
  o Business personnel and management involved in any aspect of eCTD submission design and preparation.

• Provide an overview of:
  o eCTD v4.0 terms and concepts in plain language
  o Benefits of eCTD v4.0
  o Differences to the current eCTD v3.2.2
  o High level considerations for transitioning to eCTD v4.0 from v3.2.2
Terminology/Concepts
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.

- Combination of CoU and keyword(s) defines the context.
  - If any one of them is different, the context is considered different.

<table>
<thead>
<tr>
<th>COU X</th>
<th>3.2.S Drug substance (name 1, manufacturer 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COU Y</td>
<td>3.2.S Drug substance (name 2, manufacturer 1)</td>
</tr>
</tbody>
</table>
Keyword and keyword definition

• Additional information used to organize documents within a TOC heading/section

• Keyword
  o List of allowed terms is provided.
    - e.g., list of terms for “type of control” is defined by ICH.
  o Reference to a sender-specified keyword definition

• Keyword definition
  o Sender defines list of terms.
    - e.g., company 1, company 2 for “manufacturer”
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
  o Specified by ICH
  o Specified Regionally
  o Specified by HL7
  o Specified by External Organization
  o 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
  - Media Type – to provide additional information to be used for processing the documents (e.g., study data files)
Repeating sections

- Achieved through **COU-keyword** combinations

Possible views in the tool

Module X
- mX.X CTD Heading
  - mX.X.X CTD Heading Title *(Manufacturer 1)*
  - mX.X.X.X CTD Heading Title
    - Document Title 1
  - mX.X.X CTD Heading Title *(Manufacturer 2)*
    - mX.X.X.X CTD Heading Title
      - Document Title 2

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

- Unique alphanumeric code assigned to a document
  - Does not appear in the document contents
- Used to reference the document in a context of use
- Allows the reuse of documents with a reference to the identifier instead of the resubmission of the documents
Priority number

- 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
- Refer to slide 26 for an illustration
Group title

• Keyword that can be applied to a Context of Use or Context of Use and Keyword combination to further organize content under a CTD heading

• Group title can be used when multiple documents are allowed for a Context of Use or Context of Use and Keyword combination

• The sender assigns the group title and priority number to specify how the content should appear together in a particular order

• Refer to Slide 23
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 question during the assessment of that new application.
eCTD v4.0 - Big Picture

- 3-layered Structure

```
Application

Submission |
Submission Unit |
Submission Unit |
Submission Unit |

Submission |
Submission Unit |
Submission Unit |
Submission Unit |
```
ICH eCTD – Big Picture

• Applicant submits Submission Unit 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.

ICH M8 eCTD v4.0 Orientation Material
Benefits of eCTD v.4.0

International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
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, the document may be reused by referencing its unique identifier (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., one to many, 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.
Advantages of eCTD v4.0

**Function of context groups:**
- 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

**Additional document metadata**
- Document metadata may be used to identify submission content (e.g., datasets) that require additional processing
Reuse documents previously submitted

- Unique identifier approach means documents can be referenced/reused more effectively without re-submitting the physical file
  - Across a Submission Unit (Sequence)
  - Across regulatory activities within an application
  - Across different applications
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
• Similar view on end-users' screen
• Refer to slide 26 for an illustration
Group documents

• Senders can use group title based on M4 Granularity Document where “One or multiple documents can be submitted”

• Replaces regional implementation of Node Extensions

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

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

• Change the order of documents by updating priority number.
Possible views on the tool

**Sequence 1**

- Module X
  - mX.X CTD Heading
  - mX.X.X CTD Heading Title (Ace Manufacturer)
  - mX.X.X.X CTD Heading Title

**Sequence 2**

- Module X
  - mX.X CTD Heading
  - mX.X.X CTD Heading Title (Acme Manufacturer) *displayName Updated*
  - mX.X.X.X CTD Heading Title

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

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Change document granularity

- One document replaced by many documents
- Many documents replaced by one document
- Life cycle relationship maintained on all documents
- Achieved through Context of Use life cycle
Life cycle operators

• Active, Replace and Suspend (previously New, Replace, Delete)- valid life cycle operators are still available

• Append life cycle operator omitted from eCTD v4.0
  o The applicant should take into consideration the removal of the append life cycle operator when developing a strategy for updating documents for eCTD.
Fewer system updates expected

• CTD or regional structure updates will be based on controlled vocabularies.
  o Allow implementation of changes to CTD, keywords, to be made much more easily.

• Greater flexibility to meet evolving business practices, but some system updates may be warranted
  o Business Rules may still require new logic and/or checks.
  o Updates to controlled vocabulary may require the retirement of obsolete terms.
Region-specific Implementation Topics

• Grouped submissions - One submission unit can apply to more than one application or 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.
Transition to eCTD v4.0

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

Without TMM, the applicant cannot transition to v4.0
How will transition 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 regardless of whether or not the content will undergo life cycle.
      - Exclude deleted or replaced leaves
      - Includes append leaves
    - No changes included in transition message, make changes before or afterward but not in TMM.
Purpose of the transition message

- Enable Context of Use life cycle
- Enable reuse of documents
- Want to retire v3.2.2 in the future
What does a sponsor need to consider before transitioning to v.4.0?

• Develop a strategy for managing sender-defined keywords.
  o Note this will allow for better utilization of grouped submissions when allowed in certain regions.
  o Recommend that keywords be managed across applications even though they need to be sent for each application.
  o Combine individual Study ID and Study Title keyword values.

• Develop a strategy for determining when the Transition Mapping Message warnings will restart your transition activity.

• Ensure that the Transition to v4.0 is complete before sending v4.0 message – i.e., once the first v4.0 message is received the transition process is complete.
Need tool to create v4.0 submission

- Tools required to create/manage and view eCTD v4.0
- Difficult to make manual corrections/fixes
- With eCTD v3.2.2, it was possible to manually create a pilot submission.
- eCTD v4.0 submissions much more complex to create without tools
Key Messages
Key Messages

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