CTD: Revisions to the M4 Granularity Document

CTD – Quality Implementation Working Group

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

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Outline

- **Who is the CTD-Q IWG**
- **Background**
- **Objective of the Guideline Revision**
- **Scope/Content of the Guideline Revision**
- **Implementation of the Guideline Revision**
- **Conclusion**

Background

- **1994:**
  - M2: “Electronic Standards for the Transfer of Regulatory Information” (ESTRI) EWG established
- **1997:**
  - M2: Discussed support for electronic Common Technical Document (eCTD)
- **2000:**
  - M4: “***Common Technical Document***” (CTD) finalized
  - M2: Commenced work on the electronic-CTD (eCTD)
  - M4: “***Organisation of the Common Technical Document***”

Background

- **2002:**
  - M4: "**Granularity Document: Annex to M4: Organisation of the CTD**" incorporated into "**Organisation**…" document
  - M2: eCTD Specification Version 3.0 reaches *Step 4*
- **2003:**
  - M2: eCTD v3.0 finalized
- **2004:**
  - M2: eCTD v3.2 finalized & implemented in all ICH regions

Background

- **2005:**
  - FDA started developing eCTD v4 (RPS) in HL7
- **2008:**
  - M2: eCTD v3.2.2 (current version)
- **2010:**
  - M2: Work begun on in HL7 Standards Development Organization
  - M8 spun-off from M2 to deal with eCTD
- **2016:**
  - M8: eCTD v4 reaches *Step 4*

Remit of the CTD-Q IWG*

- **Address the eCTD Change Request for the placement of "Control Strategy" (eCTD Q&A #81)**
- **Revise the M4 "ANNEX : Granularity Document":**
  - Version 3.2.2 (extant)
  - Version 4 (aka, v4, Regulated Product Submission, Next Major Version [NMV])
- **Provide input on v4 "keywords" and revisions to v3 XML-attributes****

*Implementation Working Group
** v3 XML-attributes are mapped to v4 "keywords"

eCTD version 3 & 4 compared

- **v4 implements 2-way communication**
- **Headings/subheadings mapped to:**
  - v3.2.2: XML Elements
    e.g. < m3-2-p-8-3-stability-data>.
  - v4 XML Attributes
    e.g. <contextOfUse>
    <id root="1f080afd-f5d4-4cec-8d09-2bf0ea6bec66"/>
    <code code="ich_3.2.p.8.3"
    codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
- **Headings/subheading descriptors mapped to**
  - v3.2.2: XML Attributes
  - v4: keywords

Scope of the Guideline Revision

- **Edited granularity tables:**
  - Revise extant tables
  - Add new tables for eCTD v4
- **Restricted to "Q" related sections of the "ANNEX : Granularity Document"**
  - Module 2.3 – Quality Overall Summary
  - Module 3 – Quality
- **Implemented previously published Quality-related eCTD Q&As***
- **Added appropriate explanatory text**

*Interspersed in the spreadsheet "eCTD IWG Question and Answer and Specification Change Request Document" v1.28 16 June 2016

Content of the Guideline Revision

- **Revisions begin on page 6**
- **Explains that for:**

  Modules 2.3 and 3, recommended granularity depends on the eCTD version

  Modules 4 and 5, same granularity applies to all eCTD versions
- **Directs readers to tables for:**

  eCTD v3.2.2

  eCTD v4

  Paper submissions
- **No revisions have been made to pages 13-17**

Table 1: Module 2 (paper & eCTD v3.2.2)

- **R3 Revision (2004)**
  - Acceptable: CTD documents at level S.x & P.x (e.g. S.1 and P.2)
- **R4 Revision (2016)**
  - Not acceptable: CTD documents at level S.x & P.x (which can be written at this level, but must be submitted at a higher level)
- **Current Recommendation for Quality Overall Summary**
  - A single document, *or*
  - One "S," one "P," one "A" document, *or*
  - Multiple "S," "P," and "A" documents

Table 2: Module 3 (paper & eCTD v3.2.2)

- **R3 Revision (2004)**
  - P.2 *Pharmaceutical Development* documents may only submitted at the P.2 level
- **R4 Revision (2016)**
  - P.2 Pharmaceutical Development documents may only be submitted at the P.2.x level
- **Rationale**
  - The v3 specification's **Document Type Definition** (DTD) does not permit submissions at the P.2.x level. This seems to have been unintended as the DTD was meant to conform to the pre-existing Granularity document.

Table 2: Module 3 (paper & eCTD v3.2.2)

- **R3 Revision (2004)**
  - P.4 *Control of Excipients* documents, can be rolled-up into a single P.4 document, but still may be submitted at the lower P.4.x level if needed
- **R4 Revision (2016)**
  - P.4.x documents can be rolled-up into a single P.4 document
- **Rationale**
  - The previous model sometimes resulted in many small documents with little content, e.g. where all excipients and tests are compendial

Table 2: Module 3 (paper & eCTD v3.2.2)

- **R4 Revision (2016)**
  - Addition of a new Note 3 to 3.2.S.4 and 3.2.P.5
- **Rationale**
  - Updated granularity consistent with the guidance of published eCTD Q&A# 81

Table 3: Module 2 (paper & eCTD v4)

- **Same as Table 1 for v3.2.2, except:**
- **2.3.A "Appendices" must be split into:**
  - A.1 *Facilities and Equipment*
    - New "facility" and "component" keywords added
  - A.2 *Adventitious Agents Safety Evaluation*
    - New "facility" and "component" keywords added
  - A.3 *Excipients*
- **Addition of new Notes 1-6**

Table 4: Module 3 (paper & eCTD v4)

- **R3 Revision (2004)**
  - Two color-coded categories
    - Not appropriate (yellow)
    - One or multiple documents OK (green)
- **R4 Revision (2016)**
  - Introduction of a new blue color-coded category
    - One or multiple documents OK, *except* no content roll-up from lower levels (blue)
- **Rationale**
  - Provides a location for certain special documents, such as, cross-reference to a Drug Master File, Certificate of Suitability, Control Strategy, Note to Reviewer

Table 4: Module 3 (paper & eCTD v4)

- **Similar to Table 2 for v3.2.2, except**
  - S.1 should be a single or multiple documents, and
    - Rationale: Little content expected at the S.1.x level
  - S.1.x level documents are not appropriate
    - Rationale: Additional guidance provided for the use of the new optional keywords introduced in eCTD V4, namely: facility in 3.2.A.1 (and in 2.3.A.1), component in 3.2.A.2 (and in 2.3.A.2), description in 3.2.S.7.3 and 3.2.P.8.3, container in 3.2.P.7 and excipient in 3.2.A.3
- **Additional Notes added**
  - Stability, Excipient, Container closure system, Multiple facilities

Appendices for eCTD v4 Submissions

- **Appendix A: Guidance on Using the Substance, Manufacturer, Product, and Dosage Form Keywords**
- **Appendix B: Further Explanation of "Blue" Granularity and Control Strategy Summaries**
- **Appendix C: Stability Data Guidance**
- **Appendix D: Excipient Guidance**
- **Appendix E: Container Closure System Guidance**
- **Appendix F: Guidance on Using the "Facility" and "Component" Keywords**

Appendix A: Keywords

- **Optional, only when needed, avoid "all," "N/A"**
- **Short descriptive terms**
- **Distinguish multiple**
  - Drug substances (use INN or shortened INN)
  - Manufacturers
- **"Dosage Form" keywords NOT recommended for**
  - Strengths
  - Concentrations
  - Fill volumes

Appendix B: "Blue" Granularity and Control Strategy Summaries

- **For "Blue" Granularity see slide for Table 4: Module 3 (paper & eCTD v4)**
- **Control Strategy Summaries**
  - No location specified, should note in Module 2.3
  - May be placed in one or more section, e.g.
    - 3.2.S.4 *Control of Drug Substance*
    - 3.2.P.5 *Control of Drug Product*
    - 3.2.S.2.6 *Manufacturing Process Development*
    - 3.2.P.2 *Pharmaceutical Development*
    - 3.2.S.4.5 *Justification of Specification*
    - 3.2.P.5.6 *Justification of Specification*

Appendix C: Stability Data Guidance

- **Optional for Substance and Product sections**
  - Granularity
  - Use of the "Descriptor" keyword*
- **Descriptive titles**
  - Can be used as an alternative to multiple keywords
  - Avoids splitting into multiple sections
- **Priority numbers can be assigned for sorting**
- **Additional terms can be added, e.g. orientation**

*Note: A unique single keyword value or different values from the combined use of multiple keywords for the same numbered section can generate a separate section.

Appendix D: Excipient Guidance

- **Granularity options to support business needs, e.g.**
  - A single P.4 section without lower level granularity
  - Multiple P.4 sections without lower level granularity
  - Multiple P.4 sections with P.4.x granularity
- **Considerations for granularity**
- **An optional listing of excipients may be helpful**
- **Suggestions on non-compendial excipients**
- **Excipient keyword renaming now possible**

Appendix E: Container Closure System

- **Granularity options to support business needs**
- **All CCS in one or multiple documents**
- **Use of the "container" keyword is optional**
- **3.2.P.7 can be repeated with the use of a different and unique "container" keyword value**

Appendix F: "Facility" and "Component"

- **Applies only to section 3.2.A *APPENDICES***
- **Granularity options to support business needs**
- **"Facility"**
  - Could be a geographic location or a specific building
  - Avoid redundant identical documents appearing in multiple sections
- **"Component"**
  - All adventitious agent safety data could be in one document or multiple documents within one or multiple sections
  - Multiple component products may benefit from multiple sections

Version 4 Keywords

- **All keywords are now optional (some were required in v3.2.2)**
- **Module 3**
  - ❑ substance
  - ❑ manufacturer
  - ❑ product
  - ❑ dosage form
  - ❑ excipient
  - ❑ container
  - ❑ facility
  - ❑ component
  - ❑ group title (new, used to group documents)
  - ❑ descriptor (for use in substance & product stability data)
- **Other Modules**
  - ❑ indication
  - ❑ study id
  - ❑ study title
  - ❑ site id

Thank You!