CTD: Revisions to the M4 Granularity Document

CTD – Quality Implementation Working Group

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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:
  o M2: “Electronic Standards for the Transfer of Regulatory Information” (ESTRI) EWG established

• 1997:
  o M2: Discussed support for electronic Common Technical Document (eCTD)

• 2000:
  o M4: “Common Technical Document” (CTD) finalized
  o M2: Commenced work on the electronic-CTD (eCTD)
  o M4: “Organisation of the Common Technical Document”
Background

- **2002:**
  - 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

- **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”

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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="11080afd-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"/>
    </contextOfUse>`

- Headings/subheading descriptors mapped to
  - v3.2.2: XML Attributes
  - v4: keywords
Scope of the Guideline Revision

• Edited granularity tables:
  o Revise extant tables
  o Add new tables for eCTD v4

• Restricted to “Q” related sections of the “ANNEX: Granularity Document”
  o Module 2.3 – Quality Overall Summary
  o 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 be 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
  o Drug substances (use INN or shortened INN)
  o Manufacturers
• “Dosage Form” keywords NOT recommended for
  o Strengths
  o Concentrations
  o 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
  o No location specified, should note in Module 2.3
  o 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!