

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”

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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="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

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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

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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**

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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

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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.

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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

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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

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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.

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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**

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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!