

# CTD: Revisions to the M4 Granularity Document

CTD – Quality Implementation Working Group

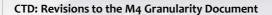
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use



CTD: Revisions to the M4 Granularity Document

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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

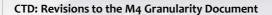
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### **Background**

- 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
  - o M2: eCTD Specification Version 3.0 reaches Step 4
- 2003:
  - o M2: eCTD v3.0 finalized
- 2004:
  - M2: eCTD v3.2 finalized & implemented in all ICH regions

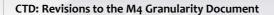
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#### **Background**

- 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"

**I**CH

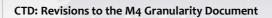
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#### eCTD version 3 & 4 compared

- v4 implements 2-way communication
- Headings/subheadings mapped to:
  - v3.2.2: XML Elementse.g. < m3-2-p-8-3-stability-data>.
  - v4 XML Attributese.g. <contextOfUse>

<id><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
  - o v3.2.2: XML Attributes
  - o 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 "<a href="https://example.com/end-specification-change-Request Document">https://example.com/end-specification-change-Request Document</a>" v1.28 16 June 2016

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#### **Content of the Guideline Revision**

- Revisions begin on page 6
- Explains that for:

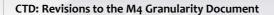
Modules 2.3 and 3, recommended granularity depends on the eCTD version

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





### 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
  - o A single document, or
  - o One "S," one "P," one "A" document, or
  - o Multiple "S," "P," and "A" documents

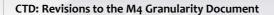
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#### Table 2: Module 3 (paper & eCTD v3.2.2)

- R3 Revision (2004)
  - P.2 Pharmaceutical Development documents may only 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

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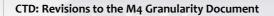
### Table 2: Module 3 (paper & eCTD v3.2.2)

#### 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





### 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

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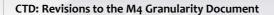
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#### Table 4: Module 3 (paper & eCTD v4)

- 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

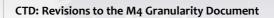
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#### **Appendices for eCTD v4 Submissions**

- 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

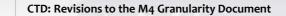
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## Appendix B: "Blue" Granularity and Control Strategy Summaries

- For "Blue" Granularity see <u>slide for Table 4: Module</u>
   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.

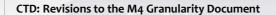
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### **Appendix D: Excipient Guidance**

- 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





#### **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

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### 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

