Regulated Product Submissions

Overview

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Goal

- Create one model that can be used for the submission of any regulated product
  - Create a framework that will allow sponsors to send regulatory information using predefined parameters to identify and catalog their content
  - Reviewers will be able to consistently locate discipline specific information

Scope

- Animal and Human products
  - Including but not limited to food additives, human therapeutics, veterinary products, and medical devices
- Worldwide use
  - Same model for all product types to all regulatory authorities

Out of Scope

- Document content will not change
  - Documentation submitted today will be the same documentation submitted tomorrow
- Business processes may not change
  - Must work within existing business processes
  - We hope since Applicants and Regulatory Authorities from varied product types are talking we can learn from each other and enhance our process as it suits our needs

Keys to success

- Keep it simple
- Flexible model that handles all regulated products
- Incorporate lessons learned from past electronic submission experience
- Multi-national Industry and Government involvement
- Promote project to raise visibility

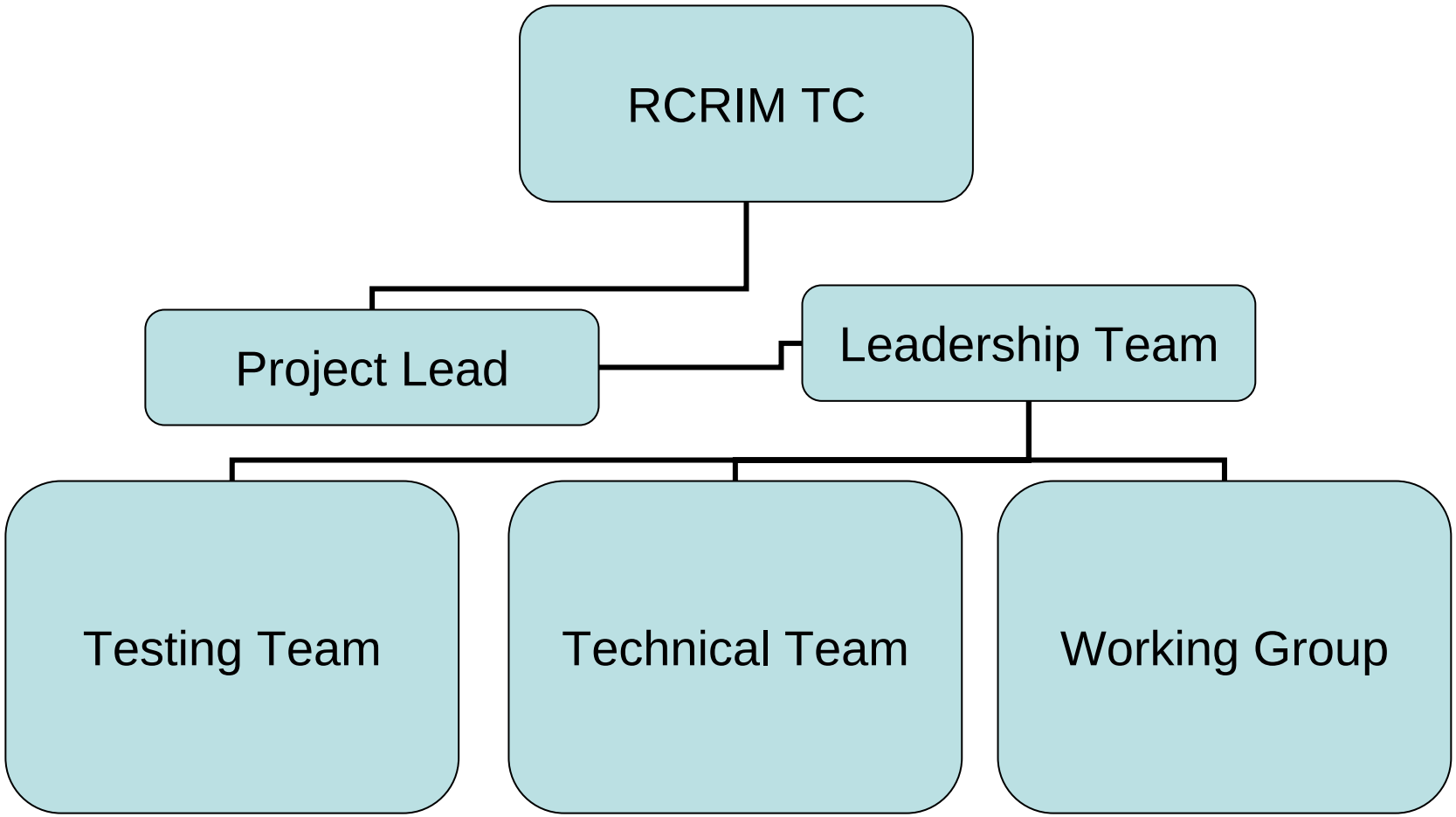
Design Decisions

- Clear communication
  - The meaning of the content that is sent is the same meaning of the content that is received
  - Submitted documentation will be clearly identified using predefined parameters
- Different predefined parameters for different submission types and regulatory authority (controlled vocabulary)
- XML catalogs the content (not intended to be read directly)

Work to date

- RPS Project initiated June 22nd 2005
  - Leveraged existing Human Pharmaceuticals experience (ICH/eCTD)
- Draft Standard for Trial Use (DSTU)
  - Ballot Passed May 1st 2006
  - 23 Storyboards (requirements for specific regulatory functions)
  - Defined 6 entities and numerous properties
  - Message model (13 Acts)
  - Documented R-MIM (introduction and walkthrough)
- Distributed sample message
- Testing kick-off June 18th 2006
- First test submission submitted to FDA Sept. 2006

Team Organization



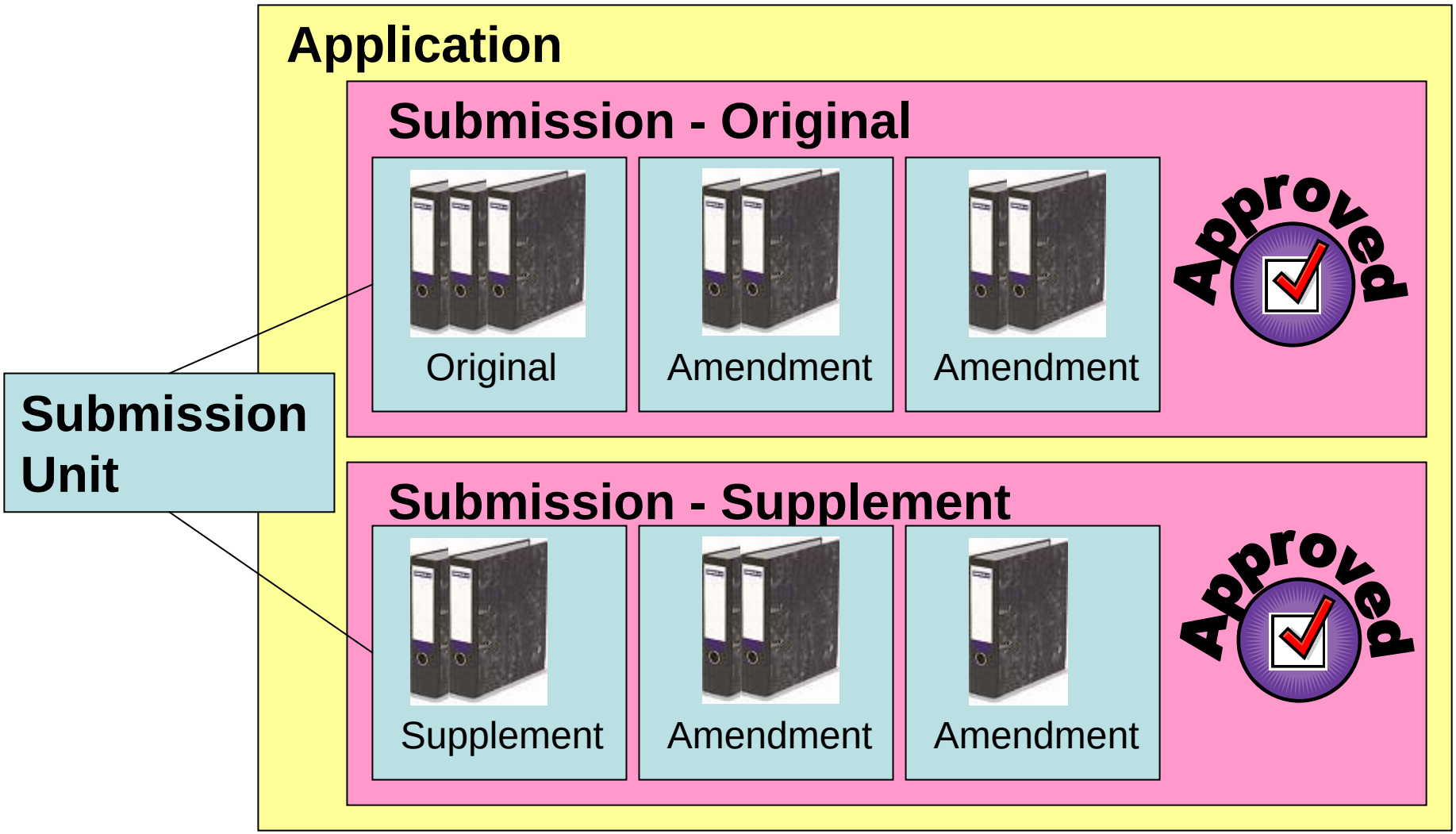
Team structure

- Project lead - reports progress back to the RCRIM TC and coordinates project activities.
- Leadership Team - facilitate and coordinate message development and testing activities, provide direction and common resolution to issues.
- Testing Team – tests the proposed standard against business requirements.
- Technical Team – provide guidance / establish standards and techniques necessary for consistent testing activities; provide common resolution to message functional issues
- Working group – determines business cases for the standard. All decisions are vetted through the working group.

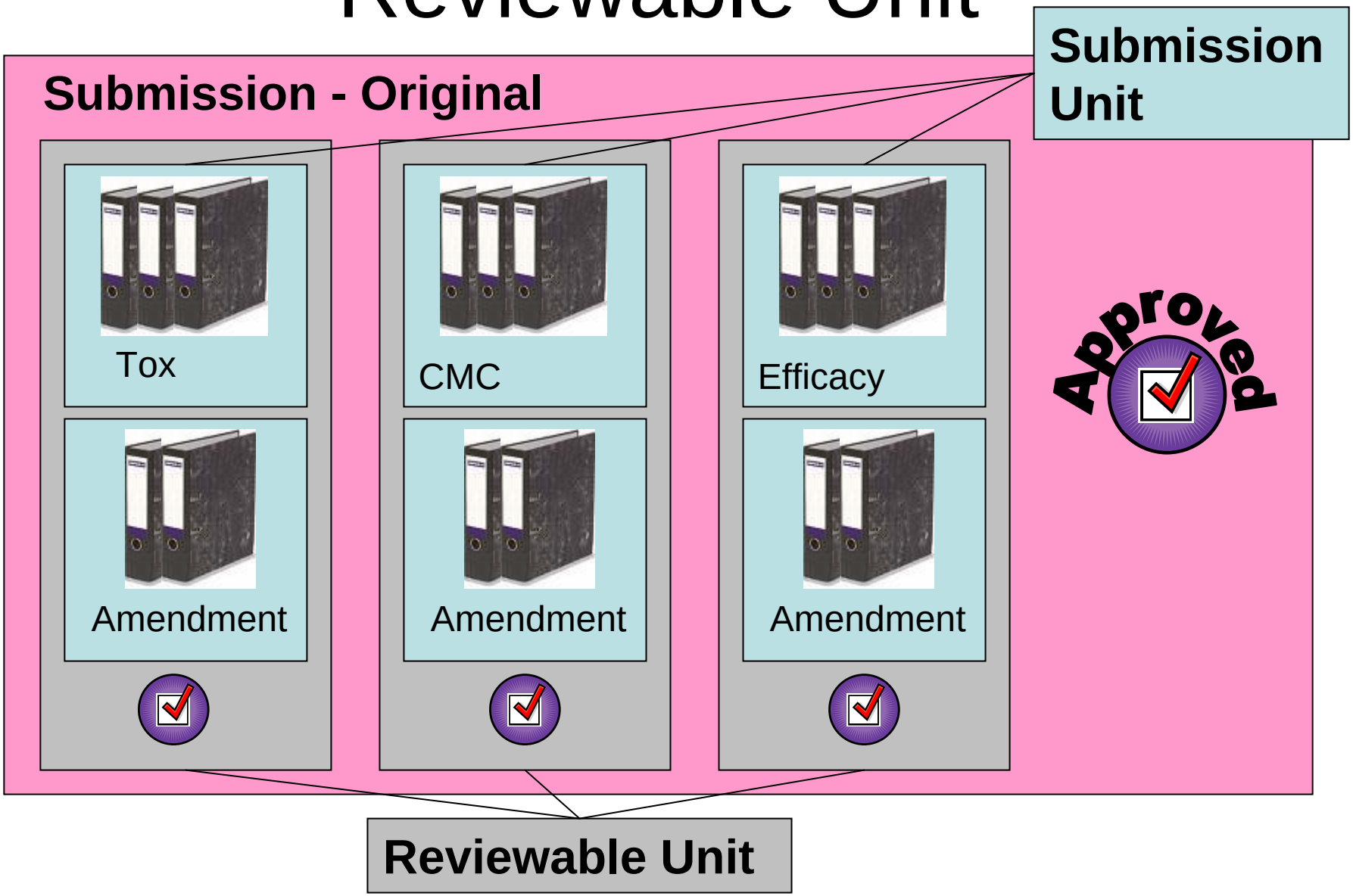
What does RPS allow now?

- Document Lifecycle
- Reuse of documents across applications
- Product/submission management
- Submission lifecycle
- Computer aided review
- Visibility into product/submission
- Allows for regional/product differences

Submission Hierarchy



Reviewable Unit



Reviewable Unit ReUse

Application

Submission Unit

Submission - Original

Tox

CMC

Efficacy

Reviewable Unit

Submission - Variation

Tox

Admin

Reusable reviewable unit is a Vet Med requirement

Context of Use

Context of Use

Submission Unit

Original

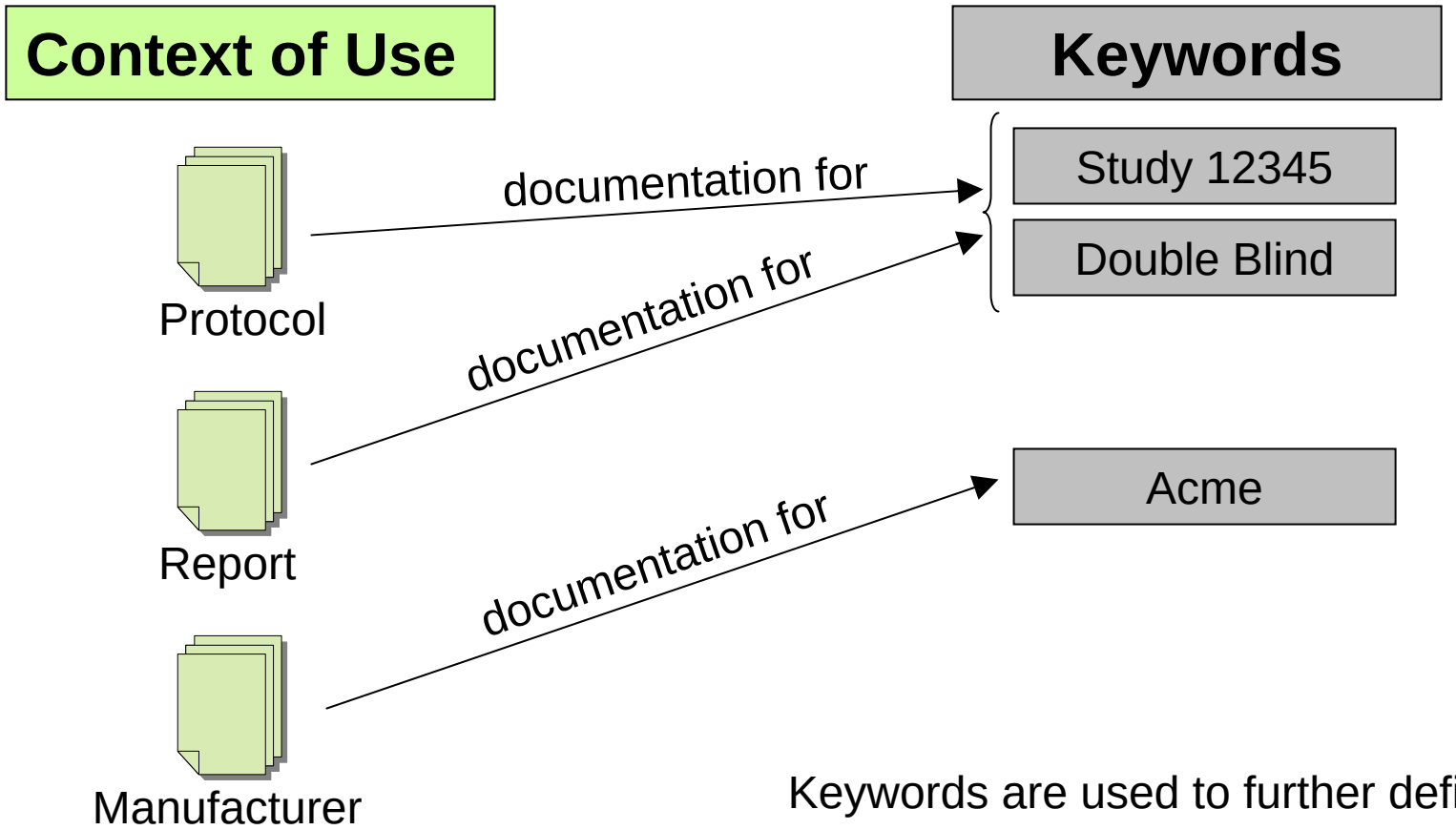
The collection of files provided to the Regulatory Authority at one time

Protocol

Intro

Report

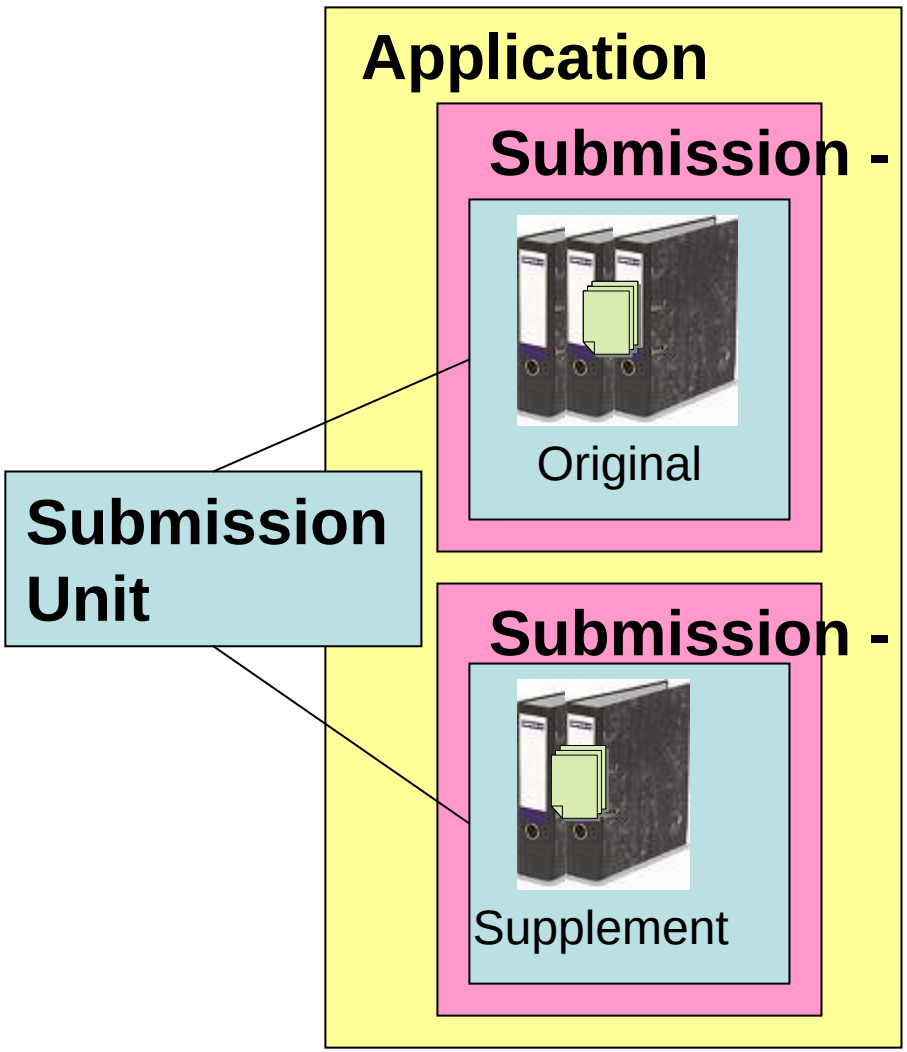
Keywords

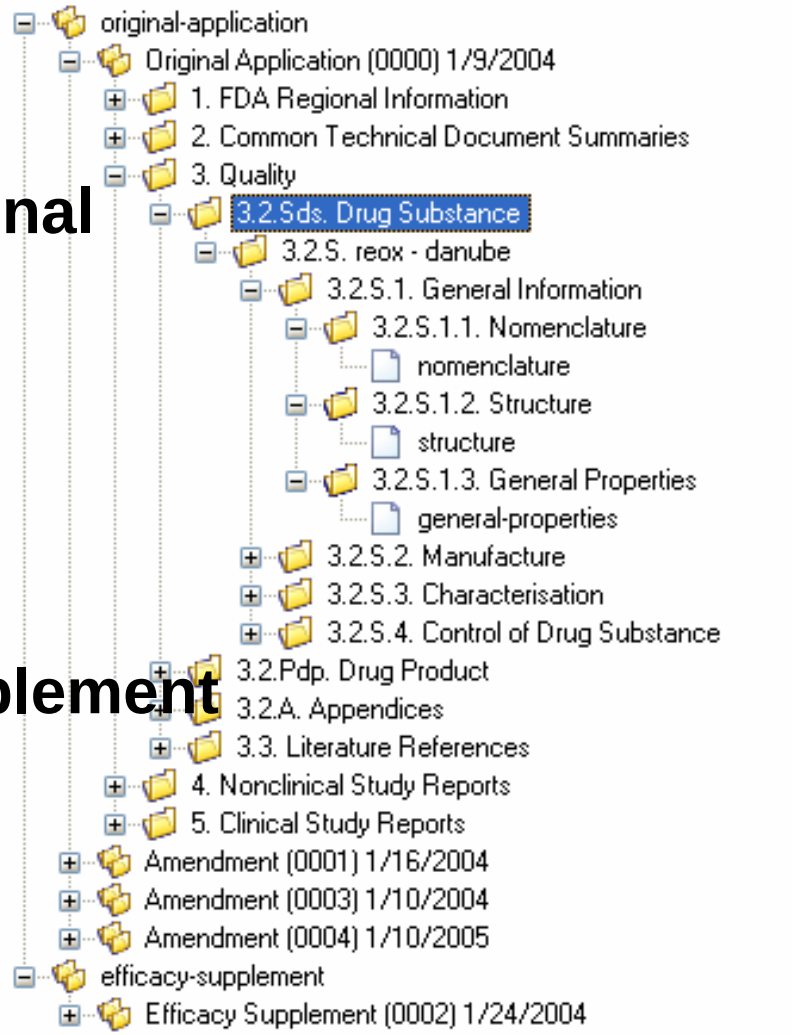


Documentation submitted to support a regulatory review

Keywords are used to further define the context of documentation. Types defined by regulatory authority (e.g. manufacturer, study), value define by business (e.g. Acme, Study 12345)

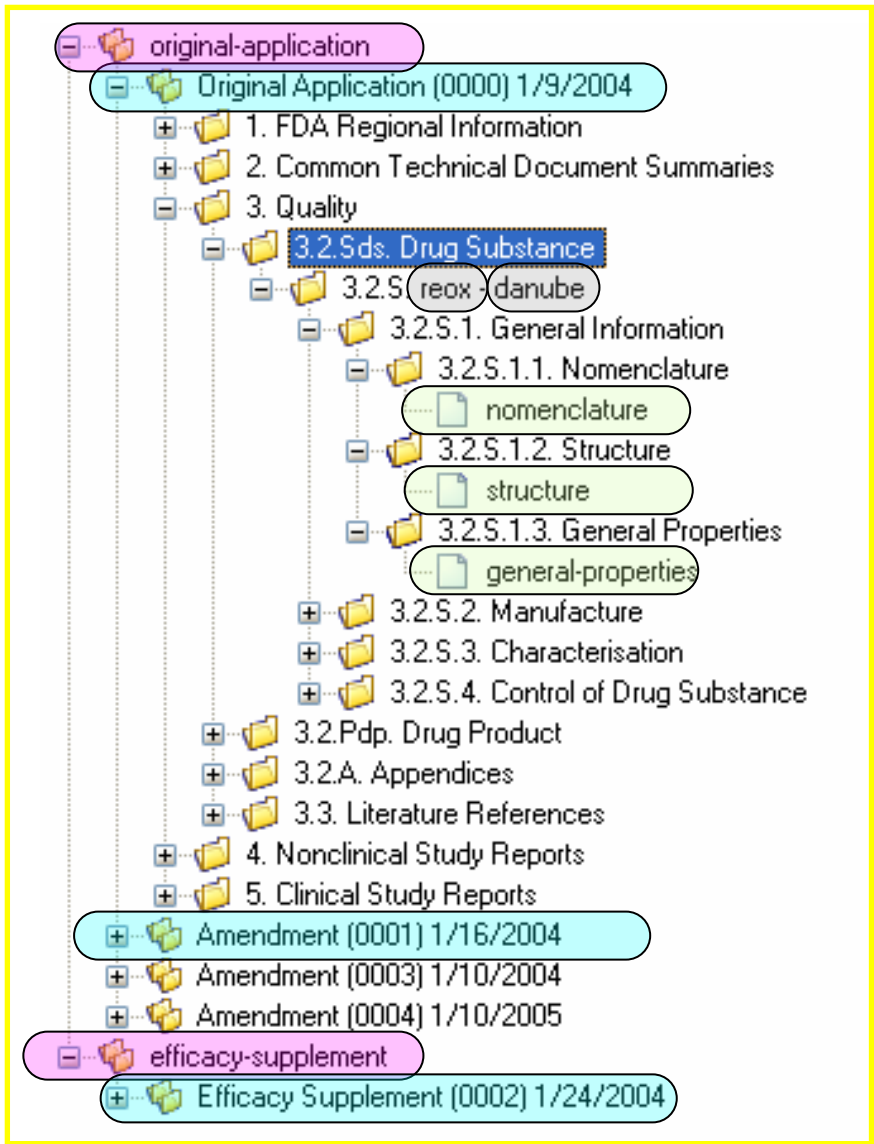
View





Keywords are used to further refine the table of contents.

View (2)



Application

Submission

Submission Unit

Keyword

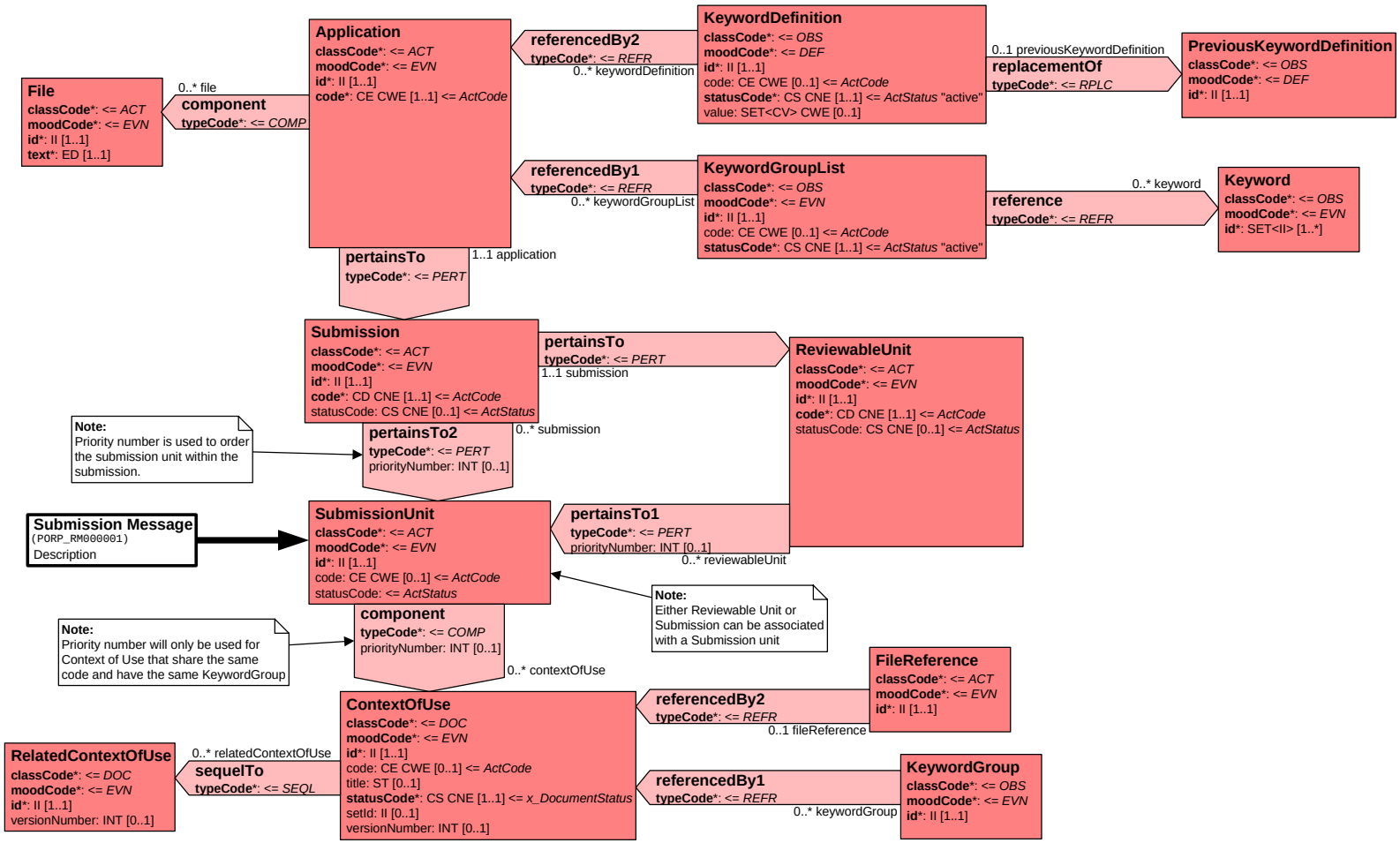
Context of Use

Reviewable Units are not shown

Submission Hierarchy

- Application
  - All submissions that are grouped together for regulatory purposes.
- Submission
  - A compilation of the contents of one or more submission units supporting a specific regulatory purpose or decision. In most cases, the compilation of the submission units is utilized in the assessment of a product's quality, safety and effectiveness.
- Submission Unit
  - The collection of files and the associated file reference information provided to the Regulatory Authority at one time. The file references are collectively called the submission unit message.
- Reviewable Unit
  - A mechanism to organize Submission Units to for the purpose of a modular review
- Context of Use
  - Regulatory processes require the submission of documents from the Applicant to the Regulatory Authority. These documents are varied in focus and are often defined by the field of study (i.e., GLP or GCP guidelines) or by the regulatory application requirements of the Regulatory Authority (e.g., Integrated Summary of Safety, Pharmacokinetics Written Summary).
- Keyword
  - Keywords are used to further define the context of documentation. For example, a piece of documentation that describe manufacturing processes would have a keyword of manufacturer.

RPS DSTU Release 1



Act / Act Relationship

- HL7 is primarily Act based
- An Act describes something that is, has, can, or is intended to be done. Therefore, Acts usually have a verb in their name. Visually, in the RMIM, the Act is a red box.
- An Act Relationship represents an association between two Acts, for example Cause/Outcome.
  - An Act Relationship is often a parent child relationship. Visually, in the RMIM, the Act Relationship is a ping pointer. The parent points to the child.
  - Each act relationship has a cardinality. (e.g. 1..* one parent has many children, 1..3 one parent has three children)

Entry Point

- Each RMIM has one entry point
- The entry point is the Act that is being sent to the recipient.
- Since industry sends a submission units to the regulatory authority, the submission unit is the entry point.
- The entry point becomes the top level element in the XML message.

Controlled vocabulary

- For differing submission types and regulatory authorities
  - Application (MAA, PMA, 510K, etc.)
  - Submission (original, supplement, etc.)
  - Submission units (original, amendment, etc.)
  - Documentation (synopsis, protocol, summary of clinical, etc.)
- Created by Regulatory Authorities (GHTF, ICH, working with industry)

Sample Instance

Controlled Vocabulary

```
- <submissionUnit>
    <id root="DB1A1DCB-7E4B-4377-BA75-48388E996C8C" />
    <code code="initial" codeSystemName="FDA" />
  - <component>
    - <contextOfUse>
        <id root="C55B5424-92AB-42b3-B2B0-A716C743EC8F" />
        <code code="RPS-Admin" codeSystemName="FDA-PMA" displayName="Administrative Information" />
        <title>Cover Letter</title>
        <setId root="C55B5424-92AB-42b3-B2B0-A716C743EC8F" />
        <versionNumber value="1" />
      - <referencedBy2>
        - <fileReference>
            <id root="A0C085DD-F851-4814-9174-350B31103E4C" />
          </fileReference>
        </referencedBy2>
      </contextOfUse>
    </component>
  - <pertainsTo2>
    - <submission>
        <id root="634B0B56-843E-462d-9B1D-95E019336378" />
        <code code="original" codeSystemName="FDA" />
      - <pertainsTo>
        - <application>
            <id root="634B0B56-843E-462d-9B1D-95E019336378" />
            <code code="PMA" codeSystemName="FDA" />
          </application>
        </pertainsTo>
      </submission>
    </pertainsTo2>
  </submissionUnit>
```

You need software

- XML is scary
- You should not create the RPS XML by hand
  - Can create the XML from you DM system
  - Can use software created from internal staff or vendor
- You should not review the XML without a viewer, including a style sheet
- There are software for free (XForms, style sheet) and for fee

Timeline (Jason’s Opinion)

- September 2007 Release 1
- September 2008 DSTU Release 2
- April 2010 Release 2

Subsequent release of standard

- Two-way communication
  - Minutes and general correspondence (related to two-way communication) including pre-submission information
- Referencing
  - in backbone (Master Files, Other submission/application, Presubmission)
  - Hyperlink content to other content
- Provide information about the submission (e.g. information currently collected on application forms)
  - information about the product
  - Contact Information
- Facility relationship (submission for a facility instead of a product)
- Work with electronic signatures

Two-way communication

- Non-documentation related information about an application (e.g., questions)
- Communication is between the applicant and regulatory authority; not individuals
- Work in existing business practices

Two-way communication storyboards

- C1. Associate a regulatory action on a submission
- C2. Associate a regulatory action on multiple submissions
- C3. Ask questions to a particular file
- C4. Ask questions to a particular logical document
- C5. Responding to a question for a regulatory authority
- C6. Ask questions to a particular application/submission/submission unit
- C7. Acknowledgment of receipt of message
- C8. Changing an amendment to a new supplement/variation
- C9. Separate a supplement to more than one submission
- C10. Communication about documentation submitted outside of the Standard
- C11. Question on non-application specific items (out of scope)

Unit of use association

- The regulated item the customer uses (e.g., model number, NDC code)
- Several unit of uses could be in consideration for approval in one submission
  - Multiple models in a PMA
  - Multiple strengths in a NDA
  - Each unit of use can potentially be approved independently
- Do we associate the unit of use at the documentation level or submission unit level?

Unit of use storyboards

- D1. Unit is added in the first sequence
- D2. New unit is added in a subsequent sequence
- D3. Unit is withdrawn
- D4. New unit is added in a supplement / variation

More Information

- HL7 Ballot packages: http://www.hl7.org/v3ballot/html/welcome/environment/index.htm
- RCRIM's TC: https://www.hl7.org/Special/committees/rcrim/index.cfm
- RPS Information Page https://gforge.nci.nih.gov/plugins/wiki/index.php?Regulated%20Product%20Submission&id=234&type=g
- HL7 tools: https://www.hl7.org/Library/data-model/V3Tooling/toolsIndex.htm