E-SUBMISSIONS

REGULATED PRODUCT SUBMISSION (RPS)

14th MARCH 2015

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INFORM · SIMPLIFY · ENABLE

AGENDA

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INTRODUCTION

RPS indicates the Health Level Seven (HL7) standard designed to facilitate the processing and review of regulated product

Also known as eCTD version 4.0. Still in draft stage

Not Restricted to Pharma but extended to Cosmetics, Food and veterinary products

BACKGROUND

The idea behind RPS and ICH's eCTD is the same—the use of a standardized format for regulatory submissions, including PDF documents and SAS datasets. Although document contents are the same for eCTD and RPS, the internal XML structures are very different

RPS will offer one of the major obvious advantage overlaps the current eCTD is to establish two-way communication between the submitter and all FDA-regulated product centres within the agency

Second, RPS will manage the life cycle of submissions by allowing cross-referencing of previously submitted information. This means that for electronic Investigational New Drug (IND) applications, New Drug Applications (NDA), and Biologic License Applications (BLAs), information need only be submitted once and previously submitted electronic documents can be applied to marketing applications.

With RPS, archived electronic IND, NDA, and BLA submissions will be retrievable through standardized automated links. Current eCTD versions lacks this cross-referencing capability

The final release in RPS is Release 3 will be headed by ICH. The ultimate goal of release three is to have more international requirements synchronising all the regulators under single umbrella , ICH.

The goal of RPS is to create an single HL7 XML message standard for submitting information to regulatory authorities. Each message includes the contents of a regulatory submission plus information such as metadata, which is necessary to process submissions.

To be implemented by late 2015 or 2016 in US and 2016 for EU.

NAVITAS

MERITS

Two-way communications: The RPS standard includes a review section which permits the product approval status to be communicated, and the context of use concept includes agency responses, including setting relationships to documents being commented on.

Updated life cycle: in the current eCTD, the submission can be segregated as an amendment belongs to an original document or a previous amendment which cannot be differentiated in the previous eCTD version.

Not Restricted to Pharma but extended to Cosmetics, Food and veterinary products.

MERITS

Document Reuse: Once a document has been submitted, eCTD v4.0 will allow for this document to be reused in the same context in a different submission unit, submission or application, reused in a different context in the same submission unit or application, or reused in a different context in a different submission unit or application. This is accomplished by assigning each document(composed on one or more files) with a unique ID that can be referenced anywhere in the Regulatory Authority's environment

Changes : eCTD v4.0 also introduces the ability to apply changes to keyword definition values, e.g., drug substance/product names, manufacturers, dosage forms, indication, and excipient without resubmitting the physical files.

RPS and eCTD

RPS

- Organize Applications and regulatory activities
- Single XML File
- Folder Structure Undefined

eCTD

- Flat structure
- Multiple XML Files
- Folder Hierarchy And Names Defined By Guidance

RPS and eCTD

RPS

- Attributes Globally Defined And Assigned At The File Level
- Attributes can be corrected

eCTD

- Attributes Assigned at Folder Level – Some At File Level
- Attributes cannot be corrected

RPS and eCTD

RPS

- **Virtual TOC:** Documents Appear In A Browse-able Structure Based Purely On Their Metadata
- Structure Created Externally By A Viewing Tool – Otherwise Only A Flat File List Would Be Seen
- Allows For Regional Or Product Differences In Organizing Documents Into A TOC

eCTD

- **Electronic TOC:** Documents Appear In A Browse-able Structure Based Largely On How Their Leaf Nodes Are Linked Into An Overall Hierarchy Of Leaves
- Structure Inherently Part Of The XML And Appears Within Any Web Browser
- Cannot Easily Add New Content For Regional Differences Or Other Regulated Products

RPS and eCTD

RPS

- Re-use documents Across Applications Formalized

eCTD

- Re-use documents Across Applications Not Formally Described And Subject To Specific Regulators' Rules

RPS and eCTD

RPS

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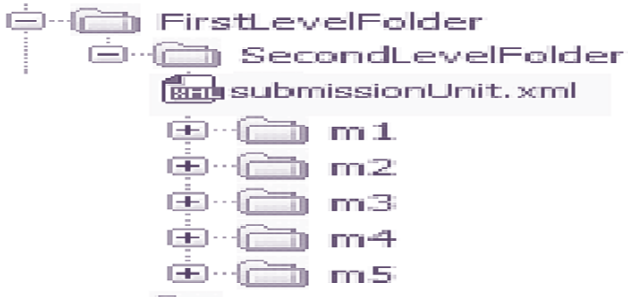
ESSENTIAL COMPONENTS

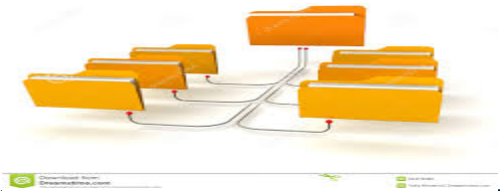
1.Files and folder
2.Controlled vocabulary
3.XML Schema
4.XML Message
5.OIDS and UUIDS
6.Data Types
7.Regional/Module 1 Implementation Guides

ESSENTIAL COMPONENTS

1.Files and folder

Files (i.e., documents referenced in the XML message) will be sent in addition to the XML message. Each file will be organized in a folder according to the structure outlined for the eCTD v4.0. Each document.text element within the eCTD v4.0 XML Message will be given a specific directory location i.e., the folders that will be used to organize the physical files if the document is being sent for the first time.





ESSENTIAL COMPONENTS

2.Controlled vocabulary

Controlled vocabularies are one of the essential components of the eCTD v4.0, which enable interoperability – i.e., clear, unambiguous communications between systems sending and receiving XML messages. For the XML components that have coded values, a controlled vocabulary will be referenced. Some of the codes are simple alphanumeric and others are based on a code system scheme for the specified code set.

RPS Code = Description
RPS established = Established
RPS-proprietary = Proprietary
RPS-chemical = Chemical

ESSENTIAL COMPONENTS

3. XML Schema

Xml schema files are required for the ICH eCTD v4.0 Message. The schemas are organized by category and sub-categories.

	Major Category	Schema Files	
1	**Core Schemas:** A common schema set for all HL7 v3 messages	infrastructureRoot-r2.xsd voc-r2.xsd datatypes-rX-cs.xsd iso-21090hl7-r2_datatypes.xsd	Referenced by core schema files: infrastructureRoot.xsd datatypes.xsd datatypes-base.xsd NarrativeBlock.xsd voc.xsd
2	**RPS Schema:** A schema set for the eCTD v4.0 – RPS compliant message	**Interactions:** PORP_IN000001UV01.xsd **Message Type:** PORP_MT000001UV01.xsd	**Control Act:** MCAI_MT700201UV01.xsd MCAI_MT900001UV01.xsd **Transmission**: MCCI_MT0001000UV01.xsd

ESSENTIAL COMPONENTS

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ESSENTIAL COMPONENTS

4. XML Message

The eCTD v4.0 message is based on the ICH eCTD v4.0 schema.

There will be one XML message created for a Submission Unit.

XML Structure

```
<PORP_IN000001UV ITSVersion="XML_1.0" xmlns="urn:hl7-org:v3"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xsi:schemaLocation="urn:hl7-
org:v3 ../../schema/PORP_IN000001UV.xsd">
    <id/>
    <creationTime/>
    <interactionId/>
    <processingCode/>
    <processingModeCode/>
    <acceptAckCode/>
    <receiver typeCode="RCV">
        <device classCode="DEV" determinerCode="INSTANCE">
            <id/>
        </device>
    </receiver>
    <sender typeCode="SND">
        <device classCode="DEV" determinerCode="INSTANCE">
            <id/>
        </device>
    </sender>
    <controlActProcess classCode="ACTN" moodCode="EVN">
    <subject typeCode="SUBJ">
```

ESSENTIAL COMPONENTS

5. OIDS and UUIDS

There are two types of unique identifiers are available in the identifier component.

Object Identifiers (OIDs)

Universally Unique Identifiers (UUIDS)

ESSENTIAL COMPONENTS

Object Identifiers

An OID is a sequence of numbers that uniquely identify an object and represent a hierarchically-assigned namespace. OIDs are formally defined using the International Telecommunications Union ASN.1 standard9. OIDS are represented as follows:

String of digits separated by periods: 2.16.840.1.113883

list of named branches: {joint-iso-itu-t(2) country(16) us(840) organization(1) hl7(113883)}

ESSENTIAL COMPONENTS

Object Identifiers

The current OIDS for the ICH domain include:

ICH-ESTRI – 2.16.840.1.113883.3.989

ICH-ESTRI-MSG-STDS – 2.16.840.1.113883.3.989.2

IN ICH ECTD V4.0, OIDS WILL BE USED TO PROVIDE THE CODE SYSTEM VALUE FOR EACH ELEMENT THAT REQUIRES A CODE. EACH REQUIRED ELEMENT WITH A CODE WILL INDICATE WHEN AN OID SHOULD BE PROVIDED.

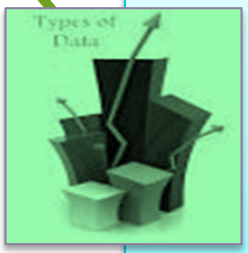
ESSENTIAL COMPONENTS

UUIDS(Universally Unique Identifiers)

A UUID is a hexadecimal number in the form of 8-4-4-4-12, including 32 digits and 4 hyphens.

UUIDs are formally defined by ISO/IEC 11578:1996 and ITU-T Rec X.667 | ISO/IEC 9834- 634

ESSENTIAL COMPONENTS



6. Data Types

Data types are another essential component of the eCTD v4.0 specification. In order to provide all of the information required in the XML message, the data types are represented as elements and attributes.

The data type for the elements and attributes are alpha /alpha numeric/ numeric/ etc.

7. Regional/Module 1 Implementation Guides

The Regional/Module 1 Implementation Guides play a key role in providing the administrative information about the submission. The administrative information is mainly found in Module 1 and, as such, is the subject of the Regional/Module 1 Implementation Guides.

ESTRI website ((http://www.ich.org/products/electronic-standards.html).

VISUAL CLUES

In the document there are several notations that are used to provide clarity to the subject matter. The first is the use of XML components (e.g. elements and attributes) versus the concept that it represents. The text will take the following notation:

- XML components
  - In narrative text, it will be Bold, Italicized text in Camel case, e.g., ***contextOfUse***
  - In XML, it will be as notated below for the XML Snippets.
- Concept without attribution to the model or message
  - Plain text with first letter capitalized as it is a defined concept, e.g., Context of Use

The following table provides visual cues that are used in the document.

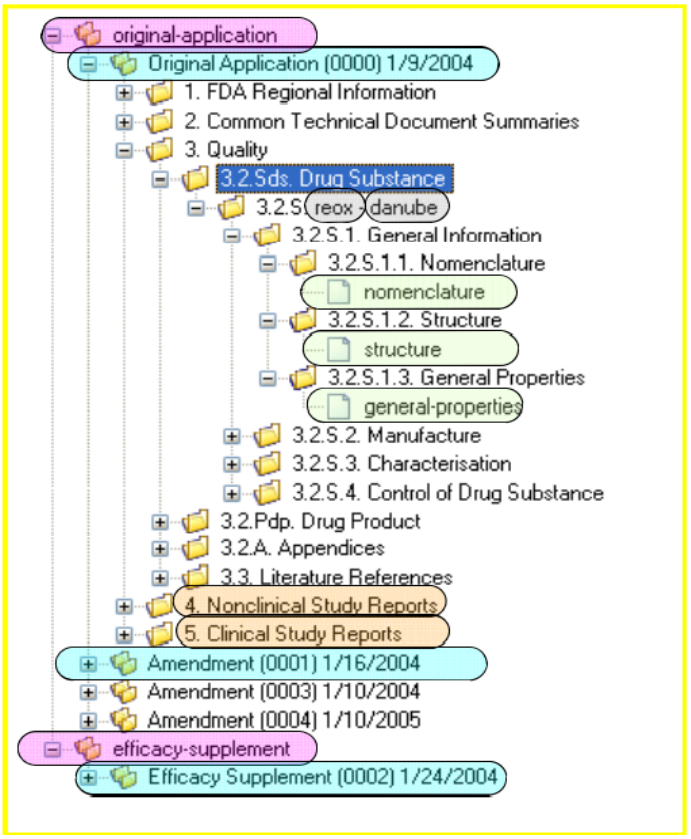
Table 1: Legend of Symbols used in Document

Icon	Description
	Technical descriptions
	Items to be careful to follow
	Additional Instructions
	References to other documents

M1 Requirements

- Added
  - Id (Company id) DUNS number
  - Submission description
  - Contact information (e.g., regulatory, technical)
  - Submission type display values
  - Submission sub-type
  - Supplement effective date
  - Cross reference application number
- Removed Date of submission

STRUCTURAL VIEW FOR TOC



Application

Submission

Submission Unit

Keyword

Context of Use

Controlled Vocabulary

Keywords are used to further refine the table of contents.

COMPONENTS FOR TOC

Application

RPS Code	Description
RPS-nda	New Drug Application
RPS-anda	Abbreviated New Drug Application
RPS-bla	Biologics License Application
RPS-ind	Investigational new drug application
RPS-dmf	Master file

Collection of related Regulatory Activities for the regulated Products. A more general term for this would be a Dossier, Ex.IND/ NDA.

COMPONENTS FOR TOC

Submission

One Regulatory Activity, consisting of a collection of Packages (which may be grouped into Reviewable Units), to support one regulatory purpose. The purpose could be a notification of a change, or a request to approve a new product or change. Ex. Original/ Amendment

Submission Unit

The collection of Documents provided by the Sponsor to the Regulatory Authority at one time A Filing or Correspondence between parties. Submission Units are components of a Submission, and may be grouped into Reviewable Units Ex- Sequence number

Reviewable Unit

Collection of one or more Submission Units grouped together (usually by subject) that collectively become part of a Submission for purpose of review ex. Case study Reports

COMPONENTS FOR TOC

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Some of the codes are simple alphanumeric and others are based on a code system scheme for the specified code set.

Document

Content, typically a file or collection of files, be it PDF or other data, provided as part of a Submission Unit.

Keyword

A Keyword is a piece of metadata or identifying information associated with a File through a reference in a Context of Use.

The Keyword Definition element belongs to the Application (Dossier). Keywords may be elements of controlled lists (such as Species, Route of Administration), or free-form text (such as Study ID).

NAVITAS

XML STRUCTURE

XML Structure

holder.applicant
informationRecipient.territorialAuthority
subject.reviewProcedure
reference.applicationReference
component.document
component.document
referencedBy.keyword
referencedBy.keywordDefinition
replacementOf.previousKeywordDefinition

```
<componentOf>
    <application>
        <id>
            <item root="" extension=""/>
        </id>
        <code></code>
        <holder>
            <applicant></applicant>
        </holder>
        <informationRecipient>
            <territorialAuthority>
                <governingAuthority>
                    <id></id>
```

application (Section 7.2.1)
Regional/Module 1 Implementation Guides, also included in this document.

holder.applicant
Regional/Module 1 Implementation

informationRecipient.territorial

XML STRUCTURE

XML Structure

holder.applicant
informationRecipient.territorialAuthority
subject.reviewProcedure
reference.applicationReference
component.document
component.document
referencedBy.keyword
referencedBy.keywordDefinition
replacementOf.previousKeywordDefinition

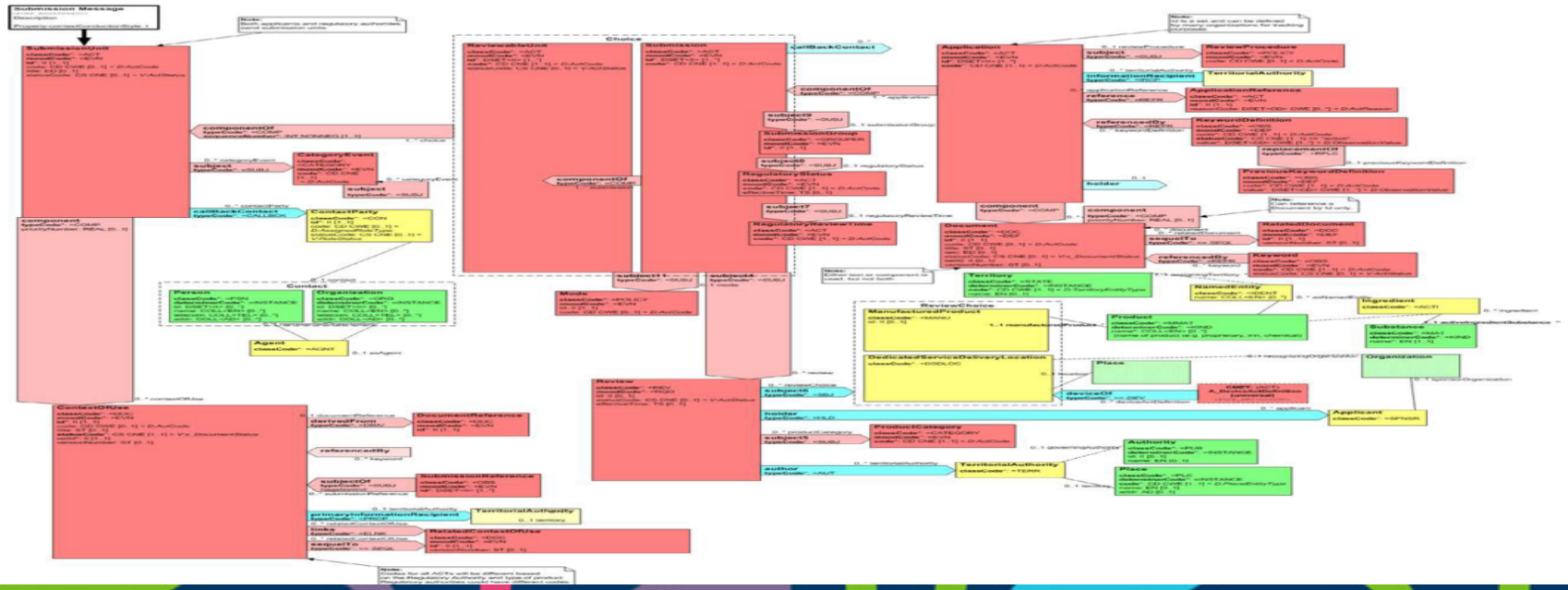
```
<componentOf>
    <application>
        <id>
            <item root="" extension=""/>
        </id>
        <code></code>
        <holder>
            <applicant></applicant>
        </holder>
        <informationRecipient>
            <territorialAuthority>
                <governingAuthority>
                    <id></id>
```

application (Section 7.2.1)
Regional/Module 1 Implementation Guides, also included in this document.

holder.applicant
Regional/Module 1 Implementation

informationRecipient.territorial

RPS Model Release 2



RPS HIGHLIGHTS

- One sequence to many product
  - E.g. Manufacturing change
- Reuse of attributes
  - E.g. fix typos
- Same standard beyond drugs
  - E.g. DDMAC
- Two way communication
  - E.g. receive letters from regulators

RPS HIGHLIGHTS

- Reuse content
  - E.g Study submitted in Investigation can be reused in marketing
- Provide contact information
- Fully support all new EU requirements
  - E.g Variation legislation

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RPS HIGHLIGHTS

- Ensure identifiers are unique
  - All sequences in all applications
- Bundled submissions
  - One sequence for many products
- Re-use of content
  - Documents and a set of document

REFERENCES

Details for the XML components and Structure can be found @- estri.ich.org/new-eCTD

http://www.fda.gov/ and

http://wiki.hl7.org/index.php?title=Regulated_Product_Submissions

Questions ?