INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH M8 Expert Working Group

ICH Electronic Common Technical Document (eCTD) v4.0
DRAFT ICH Implementation Guide v1.11

September 30, 2014

DOCUMENT CHANGE HISTORY

Version	Date	Comments
1.0	5.September.2012	Step 2 for Testing version for Steering Committee Sign-off. Included review comments from FDA Legal review. Included changes from HL7 regarding Copyright statement and Legal Notice.
1.1	17.March.2013	Updated with changes from the Step 2 for Testing lessons learnt activities.
1.2	21.April.2013	Updated with changes from Step 2 for Testing lessons learnt activities and review comments from the M8 participants.
1.3	19.May.2013	Updated with changes from review comments of version 1.2.
1.4	1.August.2013	Updated with changes to the RPS Standard (i.e., reflecting model changes) and reorganized the content to match the flow of the XML structure.
1.5	21.October.2013	Updated with changes from review comments of version 1.4 and changes to reactivation of CoU.
1.6	31.December.2013	Updated for Japanese translation.
1.7	23.May.2014	Updated with removal of Compound Documents.
1.8	30.June.2014	Updated with changes for simple document approach and model changes. Updated Appendix 1: Sample Files and Folders for Modules 2-5.
1.9	1.August.2014	Updated with changes from review comments of version 1.8.
1.10	14.September.2014	Updated with changes from vendor review and RPS R2 schema.
1.11	30.September 2014	Updated with changes from review comments of version 1.10. Review Version for M2, HL7 and FDA Lawyer.

LEGAL NOTICE

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NOTICE TO READERS

Sections of this document referencing the HL7 (Version 3) Standard, Regulatory Product Submission Release 2 Normative are used with the publisher's permission. The HL7 Standard (Version 3) Regulatory Product Submission Release 2 Normative is copyrighted by Health Level Seven International ® ALL RIGHTS RESERVED.

INSTRUCTIONS TO READER

This is a technical document that provides instructions on how to implement the eCTD v4.0 specification. The content will be provided in a consistent manner within the document. In addition, the reader may be prompted by visual cues about the context or referenced information being presented in the document.

Document Content

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 (i.e., elements and attributes) versus the concept that it represents. The document text will follow the notations described below:

- XML components
  - The document's narrative text will be bold, italicized text in camel case, e.g., ***contextOfUse***
  - The XML samples will be as notated below in the XML Snippets section.
- Concepts without attribution to the standard and/or message
  - A defined concept, e.g., Context of Use is noted in plain text with first letter capitalized.

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

Common Terms - TBD

The following table defines some common terms in this document and specific to eCTD v4.0.

Term	Definition
Document	Document will be used in the meaning of a content file representing a document required or provided to be submitted. In the eCTD v4.0 message a document will be represented by a document element referencing the file location and providing a title. The document element will be presented in its context of use. Since a document can be used multiple times, a ***documentReference*** element allows a document to be specified for the ***contextOfUse***. Each time the

	document is used in the same submission unit, that document may have a different ***contextOfUse***. The relationship is provided via the ***documentReference*** element. Accordingly, each Context of Use must reference a document.
Payload	The payload schema is the eCTD v4.0 base and it contains all of the elements in eCTD v4.0, including items from the Common Product Model and Common Message Element schema. It is organized with the following three elements in the structure: ***submissionUnit***, ***submission*** and ***application***.

XML Snippets

The following figure indicates the color coding used in the XML snippets and any meaning that should be inferred in the samples.

Table 2: Legend for XML Snippets

Text Color	Description *Sample*
Teal	Schema components *<?xml version "1.0" encoding="UTF-8"?>*
Blue	XML notations < ….= "">
Brown	XML element *id* *code*
Red	XML attribute *root* *extension*
Black	Value of the attribute or element *2.16.840.1.113883*

The following rules were used in the development of the XML samples:

- The notation of <!--....notes….-- > was used to describe conditions that should be met for an element
- The notation … [Description] … was used to indicate when there were additional elements not represented in the XML, but may be present in the actual XML message.

Note: XML editors may display these XML components differently, please use the legend above for XML presented in this document.

Location in XML

Each of the elements in this document includes a section named, “Location in XML”. The notation included uses the following convention:

Table 3: Location in XML Notation

Notation	Description	Instruction for use
>	Single arrow	The element follows the previous without indentation in the XML.
>>	Double arrow	The element follows the previous with an indentation in the XML.

For example, the following location shows both notations and is followed by the XML sample.

- ***controlActProcess***>> ***subject***>> ***submissionUnit***>>***component***>>***priorityNumber***> ***contextOfUse***

Figure 1: Element's location in XML

```
<controlActProcess classCode="ACTN" moodCode="EVN">
  <subject typeCode="SUBJ">
    <submissionUnit>
      <id root="2a6dfa61-c8bd-4d38-b421-3fc9de327f71" extension="regionally-defined"/>
      <code code="1" codeSystem="ICH SubType"/>
      <component>
        <priorityNumber value="1000"/>
        <contextOfUse>
```

Note: The priority number is represented in the path as it is a required element. In some cases optional elements will not appear in this notation. The schema will enforce any element sequencing requirements, but not optional elements. For ICH specific required elements, refer to Section 8.2 of this document.

XML Elements Tables

A table has been provided for each element in the XML message[1]. When elements have multiple element parts or attributes, they are provided in one table. When there are no attributes or values for an element, the cell is grayed out to indicate that an attribute value is required in the XML message.

Table 4: Sample XML Element Table

Table Name: <element>.<element 2>

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Conformance				
Business Rules				
Excluded Elements and/or Attributes				

Table Name: Each table is named for the elements it is representing in the XML – i.e., <element>.<element 2>. For example, the Application element has an element for the identifier, it would be represented as: ***application.id***

Element: Identifies the XML element

Attribute: Identifies the XML attribute

Cardinality: Provides information on how many times the element/attribute can be repeated in the XML message. The values in this table define the cardinality to be applied in eCTD v4.0 implementation, which sometimes restrict the cardinality defined in the schema.

Value(s) Allowed/Examples: Identifies the values allowed using simple data types and any associated examples. References to controlled vocabulary will also be provided

Description/Instructions: Provides a description of the element or attribute

Conformance: Identifies the validation requirements (e.g., XML Elements or attributes) and/or conditions that need to be met by the element

Business Rules: Identifies any business rules that are harmonized for ICH and references to Regional/Module 1 Implementation Guides when the business rules are not harmonized.

Excluded Elements and/or Attributes: Identifies elements and/or attributes that are part of the HL7 Regulated Product Submission standard and not included in the eCTD v4.0 Implementation.

[1] Further discussion is necessary to determine if any of the elements will be changed from optional to mandatory for the ICH Implementation.

1. PURPOSE

This document serves as the implementation guide and a technical specification for the Electronic Common Technical Document (eCTD) v4.0 Modules 2 through 5 using the Regulated Product Submission (RPS) Release 2 Normative.

Note to Implementers: This implementation guide will need to be used in conjunction with the Regional/Module 1 Implementation Guide, as the eCTD v4.0 message will be incomplete without all of the contents.

2. SCOPE

This document only includes the specification information for eCTD v4.0 Modules 2 – 5 submission contents which are shared across all regions. The eCTD v4.0 Regional/Module 1 content, including the Regional Administrative and Product Information, is not included in this implementation guide.

This standard defines the message for exchanging regulatory submission information electronically between Regulatory Authorities and the Pharmaceutical Industry. The XML message provides the ability to describe the contents of the regulatory exchange and all information needed to process the exchange between these two parties.

2.1 Business Case

Regulated Industry and Regulatory Authorities exchange information to address a variety of regulatory processes. The scope of the ICH activities covers the human pharmaceutical product marketing approval processes. Currently, the marketing application is provided in paper format (i.e., using the CTD) or electronic (i.e., eCTD). Frequently, when new information is provided, it directly relates to information previously submitted. During the regulatory review process as information is submitted, usually in increments, it is difficult to efficiently process and review new information in light of pre-existing information.

The goal of upgrading to eCTD v4.0 is to facilitate the processing and review of electronic regulatory submissions. The following items will be discussed in detail in other sections of this document, but are outlined below as they are the key business drivers for the next major version of eCTD:

- **Document Reuse** – the ability to submit a document once to a Regulatory Authority and refer to the document by its unique identifier in future submissions if the document is validly retained by the Regulatory Authority[2].
- **Document and Metadata life cycle** – the ability to manage the versions of documents and/or metadata.
- **Management of Document Groups** – the ability to group files together based on nature of their use (e.g., clinical study reports)

[2] Refer to applicable Regional/Module 1 Implementation Guides for specifics on document retention of regulatory submissions.

3. BACKGROUND

3.1 General Background and eCTD History

The specification for the eCTD, developed by the ICH M2 Expert Working Group (EWG), is based upon content defined within the CTD issued by the ICH M4 EWG. The structure and level of detail specified in the CTD was used to define the eCTD structure and content, but the CTD did not describe documents that can be submitted as amendments or variations to the initial application. The eCTD was defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission. The current eCTD specification is v3.2.2.

In addition, the M2 EWG developed the Study Tagging File (STF) Specification. The STF was developed to identify all of the files associated with a study to provide a mechanism to organize the content within a particular study for Modules 4 and 5. The STF is required in the United States, are not required in Europe, and are not allowed in Japan. The current STF specification is v2.6.1.

The implementation of the eCTD was done regionally and is described in the next section. Overall the eCTD was been very successful and has facilitated the ability to submit global submissions, but since the implementation of eCTD v3.2.2 there have been a number of change requests and M2 developed the next major version requirements in 2009. To address the enhancements to the eCTD specification, the M8 EWG was formed in November 2010 to specifically focus on the development and implementation of eCTD v4.0.

M8 has been actively working on eCTD v4.0 through the HL7 process to ensure that the RPS message meets ICH requirements. The RPS model now incorporates both the ICH harmonized (Modules 2 – 5) requirements and the ICH regional requirements. In September 2014 RPS V2 passed as a HL7 Normative Standard.

3.2 Implementation Experience in ICH Regions and Observer Countries

This section provides an overview of previous implementation experience of the eCTD v3.2.2. This history is provided by each ICH Region and Observer Country.

3.2.1 European Union

In the early 1990's work was initiated in Europe to develop specification-based electronic submission, the definitions developed at that time still exist today at national level. The first submission in the DAMOS format ((Drug Application Methodology with Optical Storage) was made in 1992 to the German Competent Authority (BfArM). An alternative format, called MANSEV, based on HTML and was developed in France, but was never implemented. These European formats and the work to harmonize at a European Level were superseded by the ICH eCTD specification.

The ICH eCTD specification was adopted in Europe in 2002 (ICH Step 5), this specification has now been in place for more than 10 years to submit dossiers of medicinal products for human use in electronic format. The number of submissions in this format has slowly increased over time. In 2007, due to the low level of adoption by industry and regulators, a variant format was introduced that follows the CTD structure but does not support life cycle management. This was named the non-eCTD electronic submission format (NeeS) and was considered as a stepping stone towards full

eCTD implementation.

A further step to full implementation of electronic submissions was achieved in 2005 when the EU Heads of Medicines Agencies (HMA) agreed to an EU wide initiative for all EU regulatory Authorities to be ready to accept eCTD submissions by 2010, without mandating electronic signatures. The EMA mandated electronic only submissions from 1st July 2008 and eCTD was strongly recommended for the Centralised Procedure applications from 1st July 2009. It became mandatory to submit in eCTD format for the Centralised Procedure on 1st of January 2010. Presumably, by mid-2015 the eCTD format for new applications will become mandatory in the decentralized procedure followed by 1st of January 2017 for new applications in the mutual recognition procedure.

The agreed strategy will aim for establishing secure, consistent and efficient electronic submission processes for medicinal products for human and veterinary use across the European Medicines Regulatory Network (ERMN or "the Network") which eCTD v4.0 need to support in a more broader sense.

3.2.2 Japan

Pharmaceuticals and Medical Devices Agency (PMDA) began accepting reference eCTD in 2004 and official eCTD in 2005. The number of eCTD submissions in Japan had slowly increased for several years, but the official eCTD submissions drastically increased after 2009 when eCTD v3.2.2 was implemented. Currently, the majority of new drug applications in Japan are submitted as eCTD.

3.2.3 United States

Acceptance of eCTD v3.0 submissions began at the United States Food and Drug Administration (FDA) in 2003 when the guideline/specification reached ICH Step 4 and was adopted as an ICH harmonised tripartite guideline. On September 1, 2003, FDA began accepting pilot eCTD submission for evaluation. This acceptance was indicated on August 27, 2003 by the publishing of Memo 27 in the Electronic Submissions Public Docket number FDA-1992-S-0039 and the concurrent publishing of technical specifications for eCTD submissions to FDA.

On September 13, 2007, FDA published Memo 33 which announced its readiness to accept eCTD format submission for both marketed and research regulatory applications. The memo also withdrew previous guidance that allowed for electronic submission in non-eCTD format. As of January 1, 2008, eCTD v3.x has been the preferred format for electronic regulatory submissions to FDA.

3.3 The Framework for the ICH eCTD v4.0

Since ICH's inception in 1990, the ICH process has gradually evolved. Beside the development of Tripartite ICH Guidelines on Safety, Quality and Efficacy topics, work was also undertaken on a number of important multidisciplinary topics, like MedDRA (Medical Dictionary for Regulatory Activities; ICH topic M1) or the CTD (Common Technical Document, ICH topic M4). Starting into the new millennium, the need to expand communication and dissemination of information on ICH Guidelines with non-ICH regions became a key focus, accompanied by the need to facilitate the implementation of ICH Guidelines in ICH's own regions.

In the last 10 to 15 years, more and more attention was given to the maintenance of already existing Guidelines as science and technology continued to evolve. The need to leverage with other organisations was also acknowledged, particularly for the development of electronic standards. ICH recognised the benefits afforded by collaboration with international Standards Development Organisations, from the perspective of a larger pool of technical expertise and the promising opportunity to progress ICH standards as global standards. This would also allow for extending the benefits of harmonisation beyond the ICH regions by increasing participation of non-ICH regions in guideline development.

The most desirable long-term objective is to have one globally used electronic message standard to exchange information on regulated products based on internationally approved and interoperable standards.

In 2006 a basic process description for the involvement of and collaboration with other SDOs (initially ISO, HL7 and CEN) was drafted, based on the so called “List of Critical Conditions for the SDO Message Standard Development Process”. While the same meeting, the ICH Steering Committee (SC) approved to progress the E2B (R) and M5 messages development with the SDO consortium to evaluate the SDO process.
At the ICH meeting in October 2007 in Yokohama, a decision was made to move to the next major version of eCTD specification in collaboration with SDOs instead of making slight revisions to the eCTD specification to a next minor version 3.3.3. During the ICH meeting in June 2008 in Portland, the Steering Committee endorsed that ICH would approach HL7 to discuss options to progress the eCTD Next Major Version through the Joint Initiative, a collaboration of ISO, CEN and HL7. To evaluate the acceptability of the resulting standard, ICH collected and collated requirements from each region into a draft ICH requirements document that was available after the meeting.

An ICH Expert Working Group (EWG) and Implementation Working Group (IWG) was developed to focus on the next major version of eCTD during the meeting in Fukuoka in November 2010, and the new ICH EWG/IWG M8 met for the first time as a group in June 2011 in Cincinnati.

M8 presented the concept to develop the eCTD Version 4.0 initially until step 2 of the ICH process together with HL7 as a revision of their already existing standard RPS Release 1. At this time point, the paper would be ready for giving it into an ISO fast track process with the result to become an international adopted ISO Standard. In parallel ICH M8 would continue the ICH process with the development of concepts and guidance papers for the implementation of the expected ISO standard into the world of ICH needs for regulatory exchange of information as well as a set of tests to prove the practicability of the recommendations under development. This was planned as step 3 and 4 of the ICH process and at the end to be published at the same time as the ISO standard based on the HL7 RPS Release 2 Normative standard, and the ICH eCTD v4.0 implementation guide.

3.4 Advantages of eCTD v4.0

The advantages of moving to eCTD v4.0 is to address the new requirements and/or improvements that were needed based on the implementation and usage of eCTD v3.2.2. In addition to the business drivers, the use of an international information exchange standard is needed in the regulatory environment to ensure that mandates can be issued and standardization enabled for increased

consistency across the regulatory authorities with respect to the exchange of regulatory information. The key business advantages for upgrading to eCTD v4.0 are noted below:

Harmonized submission unit: In eCTD v4.0, the harmonized and regional content is consolidated into one exchange message – i.e., all content from Module 1 through Module 5 is contained in one exchange message. The exchange message has one schema that will be used to implement the exchange of information via one submission unit – i.e., an XML file. In addition, since the schema will be shared, it will not need to be submitted with each submission unit.

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 with a unique ID that can be referenced anywhere in the Regulatory Authority's environment.

Context of Use life cycle: The Context of Use concept allows for advanced life cycle management operations. A Context of Use may be replaced by one or more Context of Use elements and vice versa (i.e., many to one) through the context of use life cycle.

eCTD v4.0 will support the existing "new", "replace", and "delete" eCTD life cycle operators; however the support for the "append" operation has been removed from the eCTD v4.0 specification.

eCTD v4.0 also introduces the ability to apply changes to keyword definition display name values, e.g., drug substance/product names, manufacturers, dosage forms, indication, and excipient without resubmitting the physical files or the Contexts of Use element. Refer to Regional/Module 1 Implementation Guide for additional information about changes to keyword definitions.

Function of document groups:
In eCTD v4.0, documents are referenced by a Context of Use, which specifies where they are to be inserted into the CTD/eCTD table of contents when presenting a reviewable structure.
One use of document groups includes the replacement for Study Tagging Files (STFs) in Modules 4 and 5 to organize multiple files relating to a single clinical study as noted in the current eCTD specification (v3.2.2). The STF was developed to address the inability of the XML backbone to provide all the metadata necessary to properly represent studies and to organize clinical study report documentation. In eCTD v4.0, the Context of Use code and Keyword combinations will function to create a group of documents.

For additional information about the technical implementation, refer to Section 8.

3.5 Change Control

Note: Need to revisit with M2 Maintenance document and controlled vocabulary.

The eCTD v4.0 specification is based on the HL7 Regulated Product Submission Standard (RPS), which was developed in the external Standards Development Organization (SDO), Health Level Seven International (HL7) and various stakeholders. Changes to the eCTD v4.0 schema[3] and

[3] The schema used for the eCTD v4.0 implementation is maintained by HL7.

resulting Implementation Guide will remain the responsibility of the ICH M8 Implementation Working Group (IWG) and will follow the established eCTD change control process. Changes that require modifications to the standard will follow established SDO's change control processes[4].

In accordance with the ICH M8 eCTD EWG & IWG Roles and Responsibilities[5], ICH M8 EWG must:

i. Ensure fidelity of ICH-Global and ICH-Regional requirements are maintained through SDO process
ii. Evaluate new requirements brought into SDO process from outside of ICH and review for utility in ICH regions and that they do not contradict ICH requirements

Change requests originating outside of the ICH M8 EWG should be brought to the attention of the ICH M8 Rapporteur upon their creation so they may be presented to the full ICH M8 EWG to be evaluated, and dispositioned.

ICH regions are encouraged to create regional processes for the creation of change requests, creation of supporting documentation, and the submission of change request packages to the ICH M8 Rapporteur when there is a need to harmonize change across the regions. These processes may be documented in Regional/Module 1 Implementation Guides and/or other regional change control documents.

Factors that could affect the eCTD v4.0 schema and Implementation Guide include, but are not limited to:

- Change in the content of the CTD, either through the amendment of information, at the same level of detail, or by provision of more detailed definition of content and structure
- Updating standards by SDOs that are already in use within the eCTD
- Identification of new standards that provide additional value for the creation and/or usage of the eCTD
- Identification of new functional requirements
- Experience of use of the eCTD by all parties

Examples of changes that would affect only eCTD v4.0 are:

- Changes to Controlled Vocabularies maintained by ICH

Examples of changes that would be needed to address evolving ICH requirements and that may affect the HL7 standards or vocabularies[6] (including the Modeling and Methodology (MnM), Infrastructure and Messaging (InM), Vocabulary and the RPS Working Groups) are:

- Changes to the Reference Information Model
- Changes to the RPS RMIM and/or referenced CMETs
- Changes to Controlled Vocabularies maintained by HL7

[4] This version of the Implementation Guide references the existing standard, RPS and its change control processes. When an ISO standard is available, this section of the document will need to be revisited

[5] M8_eCTD_Concept_Paper.pdf available on the ICH website

[6] This document references changes that may be needed during the Step 2 to meet the existing or evolving ICH requirements. This may be replaced by other processes in the future.

- Changes to Data Types used by RPS (Note: that this would also require changes to the ISO Standard, which is completed in conjunction with the HL7 processes)

Full details of the ICH change control management process are described in an external document titled, *Change Control Process for the eCTD*[7]. Refer to the Regional/Module 1 Implementation Guide for additional information about changes to the regional implementation information.

4. COMPONENTS OF THE ECTD V4.0

This section will provide a brief overview of the essential components of the eCTD v4.0 specification. The essential components include:

- OIDS and UUIDS (summarized in Section 4.5)
- Data Types (summarized in Section 4.6)
- Regional/Module 1 Implementation Guides (summarized in Section 4.7)
- Files and Folders (detailed information provided in Section 5)
- Controlled Vocabulary (detailed information provided in Section 6)
- ICH eCTD v4.0 XML Schema (detailed information provided in Section 7)
- eCTD v4.0 XML message (detailed information provided in Section 8)
- Forward Compatibility (detailed information in Section 10)
- Validation Rules (detailed information in Section 12)

Note: Reference the ESTRI Website for complete list of documents in the ICH eCTD v4.0 Implementation Package.

Each of these components is detailed in the subsequent sections to include specific information about the component's role in the implementation of the specification. In order to compose a complete eCTD v4.0 compliant message, the contents of this implementation guide will need to be complemented by several other documents. The focus of this document is to outline the essential components of the eCTD v4.0 and specifically the information required to compose Modules 2 – 5 of the CTD.

4.1 Files and Folder

The 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 structure as 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. For detailed information on this topic, refer to Section 5 below.

4.2 Controlled Vocabularies

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 elements that have coded values, a controlled vocabulary will be required to indicate the value of the concept. Each code has a code system. The code system may be managed by ICH, Region or the Applicant.

[7] All ICH eCTD change control documentation can be found on the ich.org or estri.org websites.

Controlled vocabularies are defined external to the message; a code is used as the identifier to convert the code value into the meaningful terms that will be used in any system that implements the viewing of the information sent in the XML message. The controlled vocabularies are detailed in Section 6 and examples are given for the applicable XML components.

For Controlled Vocabularies that will be maintained by ICH, the Expert Working Groups M8 and M2 will work on establishing governance of the eCTD v4.0 controlled vocabulary[8]. All other controlled vocabularies will be maintained by each Regulatory Authority or designated External organization.

Consult Regional/Module 1 Implementation Guide for additional information about the maintenance of Regional Controlled Vocabulary identified in Section 6.2 below.

4.3 ICH eCTD v4.0 XML Schema

This section will outline the required schema files for the ICH eCTD v4.0 Message. The schemas are organized by category and sub-categories in the table below. The schemas below will be provided on the ESTRI website.

	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_IN000001UV.xsd **Message Type:** PORP_MT000001UV01.xsd	**Control Act:** MCAI_MT700201UV.xsd MCAI_MT900001UV.xsd **Transmission**: MCCI_MT000100UV.xsd
		Referenced Schema Files	

[8] Refer to the Estri website for additional information

	Major Category	Schema Files	
3	**Common Product Model Schema:** The Common Product Model schemas referenced by the RPS Schemas.	POCP_MT010100UV.xsd POCP_MT010200UV.xsd POCP_MT010300UV.xsd POCP_MT010400UV.xsd POCP_MT010600UV.xsd POCP_MT020100UV.xsd POCP_MT020200UV.xsd POCP_MT030100UV.xsd POCP_MT030200UV.xsd POCP_MT030300UV.xsd POCP_MT040100UV.xsd POCP_MT050100UV.xsd POCP_MT050200UV.xsd POCP_MT050400UV.xsd	POCP_MT060000UV.xsd POCP_MT060100UV.xsd POCP_MT060200UV.xsd POCP_MT070000UV.xsd POCP_MT070100UV.xsd POCP_MT070200UV.xsd POCP_MT080200UV.xsd POCP_MT080300UV.xsd POCP_MT081100UV.xsd POCP_MT082100UV.xsd POCP_MT090100UV.xsd
4	**Common Message Elements Schema:** The CMETs referenced by the Common Product model or RPS Schemas	COCT_MT030203UV07.xsd COCT_MT040203UV09.xsd COCT_MT050002UV07.xsd COCT_MT070000UV01.xsd COCT_MT090100UV01.xsd COCT_MT090108UV.xsd COCT_MT090300UV01.xsd COCT_MT090303UV01.xsd	COCT_MT150000UV02.xsd COCT_MT150003UV03.xsd COCT_MT240003UV02.xsd COCT_MT440001UV09.xsd COCT_MT710000UV07.xsd COCT_MT960000UV05.xsd COCT_MT150007UV.xsd

4.4 The eCTD v4.0 XML Message

The eCTD v4.0 message is based on the ICH eCTD v4.0 schema and has only been constrained where noted in this Implementation Guide or the Regional/Module 1 Implementation Guides. There will be one XML message created for a Submission Unit.

Consult Regional/Module 1 Implementation Guide for additional information about the composition of the XML message.

4.5 OIDS and UUIDS

There are two types of unique identifiers, Object Identifiers (OIDs) and Universally Unique Identifiers (UUIDs). The subsections below provide additional information on how they are used by ICH eCTD v4.0. Refer to Regional/Module 1 Implementation Guides for regional use of OIDs or UUIDs.

4.5.1 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 standard[9]. 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)}

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
- ich-estri-msg-stds-m8-ectd-step2 – 2.16.840.1.113883.3.989.2.2.4
- ich-estri-msg-stds-m8-ectd-step2-code-lists – 2.16.840.1.113883.3.989.2.2.4.1

In ICH eCTD v4.0, OIDs will be used to provide the codeSystem value for each element defined by ICH that requires a code. Each required element with a code will indicate when an OID should be provided. Code systems managed by regions or external organizations will have a registered OID.

4.5.2 Universally Unique Identifiers

A UUID is a hexadecimal number in the form of 8-4-4-4-12, including 32 digits and 4 hyphens.[10] UUIDs are formally defined by ISO/IEC 11578:1996 and ITU-T Rec X.667 | ISO/IEC 9834-8:2005. UUIDs are represented as follows:

- String of digits separated by hyphens: 25635f23-a3a4-4ce0-9994-99c5f074960f

In ICH eCTD v4.0, UUIDs will be used for any identifier root attribute value. Each required element with an identifier (e.g., id) will indicate when a UUID should be provided.

4.6 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 as follows:

- Alpha – allowing only alpha characters to be used (e.g., language – en, jp, etc.)
- Alpha Numeric – allowing alpha, numeric and special characters[11] to be used in a string. XML should follow W3C standards for alpha numeric values.
- Numeric – only allows numeric characters (e.g., 0 through 9.E+-) to be used in a string for integers and real numbers.
- Boolean: allows a true or false value to be provided.

---

[9] International Telecommunication Union, x680: Information technology – Abstract Syntax Notation One (ASN.1): Specification of basic notation

[10] International Telecommunication Union, x667: Information technology – Open Systems Interconnection – Procedures for the operation of OSI Registration Authorities: Generation and registration of Universally Unique Identifiers (UUIDs) and their use as ASN.1 object identifier components

[11] See Section 5.2.1 for allowable special characters

- nullFlavors: these are used when required values need to be left blank. Null flavors are based on HL7 Messaging standard, and constraints will be mentioned for each XML element.[12] Currently, null flavors are not used in eCTD v4.0.

Note: The data types for HL7 RPS are specified by ISO 21090: Health informatics -- Harmonized data types for information interchange, however the usage in the eCTD v4.0 Implementation guide refer to the corresponding XML elements or attributes, and the values follow the simple data types as explained above.

4.7 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 main subject of the Regional/Module 1 Implementation Guides.

Note to Implementers: *The information in this ICH eCTD v4.0 Implementation Guide is necessary, but not sufficient for creating the complete XML message for transmission. The Regional/Module 1 Implementation Guides are required to send a complete XML message.*

The Regional/Module 1 Implementation Guides will be available through the ICH ESTRI website (http://www.ich.org/products/electronic-standards.html).

4.7.1 Region-Specific Elements

The elements and business rules that are Region/Country specific will be covered by each of the Regional/Module 1 Implementation Guides, as applicable:

- ***application***
  - ***subject.reviewProcedure***
  - ***reference.applicationReference***
  - ***holder.applicant***
  - ***informationRecipient.territorialAuthority***
- ***submission***
  - ***subject.submissionGroup***
  - ***subject.regulatoryReviewTime***
  - ***subject.Mode***
- ***review***

[12] All of the rules for required elements are not known. Placeholders are provided in this version of the draft Implementation Guide as it is an issue that needs to be addressed by ICH M8.

- ***subject.regulatoryStatus***
- ***subject.productCategory***
- ***subject.manufacturedProduct***
- ***holder.applicant***
- ***author.territorialAuthority***

Consult Regional/Module 1 Implementation Guides for additional information about Region/Country the included elements and for specific conformance and business rules for the relevant elements.

4.7.2 ICH Excluded Elements

The following elements are excluded from ICH eCTD v4.0 and should not be sent in the XML message.

- ***Document***
  - ***referencedBy.Keyword***
- ***Submission***
  - ***subject1.regulatoryStatus***

Consult Regional/Module 1 Implementation Guides for additional information about Region/Country specific excluded elements.

4.7.3 Excluded Business Processes

This document will not address any regional business processes. The regional business process(es) may include, but are not limited to the following:

- **Two-way Communication** – includes information on Regulatory Authority communication with the Applicant.
- **Dossier Management/Submission Life Cycle** – includes rules for Submission Unit, Submission and Applications.
- **Submission Units with Multiple Submission components** (e.g., Grouped Submissions and Group Variations) – includes rules for sending submission units that will reference more than one submission component.

Consult Regional/Module 1 Implementation Guides for additional information about Region/Country specific excluded business processes.

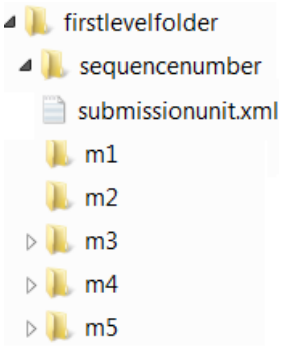
5. SUBMISSION CONTENTS, FOLDER AND FILE STRUCTURE

The folder and file structure specified for the document contents being transmitted along with the XML message will need to follow various specifications and rules as presented below in this section.

5.1 Submission Unit Contents

When submitting the contents of a Submission Unit, the following structure should be used:

Figure 2: Submission Unit Folder Structure



The *First Level Folder* will be determined by Region/Country and additional information can be found in the Regional/Module 1 Implementation Guides.

The *Second Level Folder* should be the same for all regions and named with the "*sequence number"* of the submission unit i.e., the actual value of the sequence number e.g., 999 (Refer to Regional/Module 1 Implementation Guides for additional information when there is more than one submission in the submission unit). The following contents should be included in the Second Level Folder:

- ICH eCTD v4.0 XML Message for an individual Submission Unit, named "submissionunit.xml". **Note**: the sender should not send the schema files – i.e., the util folder is no longer required, the XML should reference the interaction schema being used, see Section 8.1.
- Folders for Modules 1 – 5 and the content to be included in that submission unit. The following rules may apply to the contents:
    - Folder structure for m1 folder should follow each Regional/Module 1 Implementation Guide
    - Folder structure for m2-m5 folders should follow the structure provided in this document, see Sections 5.4 and 11.[13]
    - All files included in these folders should be accounted for in the XML message[14]
    - Files previously sent do not need to be sent again[15]

[13] Consult Regional/Module 1 Implementation Guides for any exceptions to this rule.

[14] *Ibid.*

[15] *Ibid.*

5.2 Naming Conventions

The naming convention for folders was modified for the eCTD v4.0 implementation. Refer to Section 11 for the complete folder naming conventions for Modules 2-5.

Additional guidance for naming convention that is not specified in the sub-sections includes:

- Folder and file names should be written in lower case only.
- All files should have one and only one file extension.
- The file extension should be used to indicate the format of the file.
- The First Level Folder should follow details of the respective Regional/Module 1 Implementation Guide.

5.2.1 Allowable Characters

All implementations shall follow the IETF rules for Uniform Resource Locators (URLs) (except for period and asterisk) for file or folder name. The special characters indicated in the table below may be used.

Figure 3: Allowable Special Characters

Special Character	Description
$	Dollar sign, Peso sign
-	Hyphen, Dash
_	Underscore, understrike, low line, low dash
+	Plus sign
!	Exclamation mark
'	Apostrophe, Single quotation mark
(	Left parentheses, Left bracket (UK)
)	Right parentheses, Right bracket (UK)

Consult the IETF documentation on *Uniform Resource Identifier (URI): Generic Syntax RFC 3986.*

Consult Regional/Module 1 Implementation Guide for a full list of allowable characters.

5.2.2 Length

The restrictions on file or folder name lengths should follow the specifications below:

- Maximum document (i.e., file) name length: 64 (including file name extension)
- Maximum folder name length: 64
- Maximum path length including first level folder: 180
    - *Note: this allows the folder structure to exist under a logical drive with high level folder that is applicable to the submitter's environment*
- File name extension = 3 or 4 characters

5.3 Pathname Conventions and Best Practices

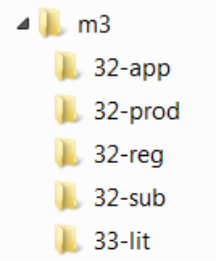
The pathname convention should reference the relative folder path using the forward slash (/) character to separate the folders. For example, the following pathname indicates the location of the file relative to the submissionunit.xml file e.g.,"m2/23-qos/introduction.pdf".

Consult Regional/Module 1 Implementation Guide for additional information on folder path references.

5.4 Folder Hierarchy

Following the naming and pathname conventions above, the actual physical structure of the folder hierarchy should follow the guidance in Section 11 and Regional/Module 1 Implementation Guide. An example for Module 3 is depicted in the following figure.

Figure 4: Sample Folder Hierarchy of Module 3



Refer to Section 11 for the complete folder hierarchy for Modules 2-5.

Note: Sub-folders within a folder should not exceed 25 folders and there should be no more than seven (7) levels of folders (i.e., nesting greater than 6 levels is not acceptable) within the Second-Level Folder.

This allows a cushion before exceeding the limit of 8, as specified by ISO9660. This allows the additional folders that may be needed in the sender or receiver's file directory.[16]

5.5 File Formats

In the eCTD v4.0 message, file formats are not specified. Consult Regional/Module 1 Implementation Guides for additional information about what file formats will be accepted.

5.6 Checksums

The eCTD v4.0 XML message will contain checksums for all ***Document.text.integrityCheck*** elements. The SHA-256 integrity check algorithm should be applied to obtain a checksum for all files referenced in a ***document*** element within a given submission unit.

The purpose of the checksum is as follows:

[16] This is still an issue for this draft version of the Implementation Guide.

- The integrity of each file can be verified by comparing the checksum submitted in the XML message and a computed checksum by the receiving system.

- The checksum can be used to verify that the file has not been altered in the historical archive of the Regulatory Authority.

5.7 Compressed Archive

A compressed archive is any collection of files that have been added to an archive and the archive has been compressed to minimize the file size of the archive file (e.g., zip files and tar.gz files). There should not be any compressed archives submitted for content in Modules 2 to 5.

Consult Regional/Module 1 Implementation Guides for a full list of allowable file compression archive formats.

6. CONTROLLED VOCABULARIES

As described in Section 4.2, there is extensive use of controlled vocabularies in the execution of an eCTD v4.0 message. The information in the following sub-sections will outline the controlled vocabulary used in developing an eCTD v4.0 message. There are several different authoritative sources for the controlled vocabulary, and as such they are categorized below by the organization that controls the content. The ICH eCTD v4.0-specific terminology – i.e., the controlled vocabulary determined by ICH are listed in Section 6.1.

Note to Implementers: *During Step 2, the controlled vocabulary will be provided both as genericode files and spreadsheet format.*

6.1 Controlled Vocabularies specified by ICH

The controlled vocabularies specified by ICH M8 for eCTD v4.0 are provided below with a brief description of the terminology and location for obtaining detailed information.

- eCTD v4.0 – Context of Use Codes: Specifies the code set for the Context of Use values that will represent the headings found in the CTD structure.

Consult Regional/Module 1 Implementation Guide to complete the list of allowable Context of Use vocabulary.

- eCTD v4.0 – Keyword Codes: Specifies the keyword types that have a controlled vocabulary (e.g., species, route of administration, duration and type of control).

Consult Regional/Module 1 Implementation Guide to complete the list of of allowable Keyword Definition vocabulary.

- eCTD v4.0 – Keyword Definition Codes: Specifies the keyword codes for the types of keywords that are defined by ***keywordDefinition*** (e.g., manufacturer, dosage form, substance, indication).

Consult Regional/Module 1 Implementation Guide to complete the list of allowable Keyword vocabulary.

6.2 Controlled Vocabularies specified Regionally

The controlled vocabularies specified by each Region for eCTD v4.0 are provided below. The ***codeSystem*** OIDs for each of the codes sets will be defined in Regional/Module 1 Implementation Guides.

- eCTD v4.0 – Application Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Application vocabulary.

- eCTD v4.0 – Application Reference Reason Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Application Reference Reason vocabulary.

- eCTD v4.0 – Category Event Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Category Event vocabulary.

- eCTD v4.0 – Contact Party Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Contact Party vocabulary.

- eCTD v4.0 – Context of Use Codes: Specifies the code set to represent the headings found in the CTD structure that are specified by regional authorities (specifically Module 1).

Consult Regional/Module 1 Implementation Guide for a full list of allowable Context of Use vocabulary.

- eCTD v4.0 – Keyword Codes: Specifies the keyword types that have a controlled vocabulary, which may be additionally specified by regional authorities.

Consult Regional/Module 1 Implementation Guide for a full list of allowable Keyword vocabulary.

- eCTD v4.0 – Keyword Definition Codes: Specifies the keyword codes for the types of keywords that are specified by regional authorities.

Consult Regional/Module 1 Implementation Guide for a full list of allowable Keyword Definition vocabulary.

- eCTD 4.0 – Ingredient Role Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Ingredient Role Code vocabulary.

- eCTD v4.0 – Manufactured Product Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Manufactured Product vocabulary.

- eCTD v4.0 – Mode Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Mode vocabulary.

- eCTD v4.0 – Place Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Place vocabulary.

- eCTD v4.0 – Product Category Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Product Category vocabulary.

eCTD v4.0 – Regulatory Status Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Regulatory Status vocabulary.

- eCTD v4.0 – Regulatory Review Time codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Regulatory Review Time vocabulary.

- eCTD v4.0 – Review Procedure Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Review Procedure vocabulary.

- eCTD v4.0 – Submission Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Submission vocabulary.

- eCTD v4.0 – Submission Unit Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Submission Unit vocabulary.

- eCTD v4.0 – Substance Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Substance vocabulary.

- eCTD 4.0 – Territorial Authority Role Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Territorial Authority Role Code vocabulary.

- eCTD 4.0 – Territorial Codes

Consult Regional/Module 1 Implementation Guide for a full list of allowable Territorial Code vocabulary.

6.3 Controlled Vocabulary specified by HL7

The controlled vocabularies specified by Health Level 7 (HL7) are provided below with a brief description of the terminology and location for obtaining detailed information.

- **HL7 Document Type Codes:** This vocabulary is provided in the HL7 version 3 Standard for the ***typeCode*** attribute on certain elements within the XML message. These codes are only required for ***typeCode*** attributes that are not fixed in the XML Schema. The ***codeSystem*** OID (2.16.840.1.113883.5.1002) is not required in the XML message for any ***typeCode*** attribute.

- **HL7 Status Codes:** This vocabulary is provided in the HL7 version 3 Standard for the ***statusCode*** element part on various elements within the XML message. These are values that should be used in the XML message for ***statusCode.code***. The ***codeSystem*** OID is not required for the statusCodes. Note: Status codes can only use the values provided by HL7 (e.g., ***codeSystem*** OID: 2.16.840.1.113883.5.14).[17]

Note to Implementers: *The controlled vocabulary required by the HL7 RPS standard enables system to system communications and is not always the ideal way to display concepts in a system graphical user interface (GUI). Be cautious not to apply the technical codes in the GUI, instead use the business friendly terms that are specified by Regulatory Authorities in the Regional/Module 1 Implementation Guides.*

6.4 Controlled Vocabulary specified by Others

The controlled vocabulary specified by other organizations (i.e., not managed by ICH, Region or HL7) are provided below noting the responsible organization, a brief description of the terminology and location for obtaining detailed information.

- **International Organization for Standardization (ISO) - Two-Letter Language Code**: This is a two letter code that is specified for the language as specified in the ISO 639.1 standard. This vocabulary is used to define the ***text@language*** attribute. The ***codeSystem*** OID for two-letter language code is 1.0.639.1.

[17] The allowable value set varies by element in the HL7 RPS R2 standard, for specifics of the ICH eCTD v4.0 Implementation, consult the controlled vocabulary artifacts.

- **ISO Country Code – Two-letter Country Code:** This is the Country code that is specified in the ISO 3166-1 standard. The ***codeSystem*** OID for the two-letter Country code is 1.0.3166.1.2.2.

7. ICH eCTD v4.0 XML Schema

7.1 Core Schema

The core schemas will be the foundation for the ICH eCTD v4.0 XML schema. These schemas will not be referenced directly, but indirectly by each other and in the referenced ICH eCTD v4.0 schemas.

7.1.1 InfrastructureRoot-r2

This schema defines the properties that are valid for all elements in all other schemas.

Note: The elements in this schema are not directly referenced in this implementation guide.

7.1.2 iso-21090hl7-r2_datatypes

This schema provides the ISO-21090 datatypes, which are used to define the elements and attributes. This file defines the composition of the ISO-21090 datatypes within the schema and is included in the infrastructure root schema.

Note: The elements in this schema are not directly referenced in this implementation guide.

7.1.3 Voc-r2

This schema provides the vocabulary items that are part of the standard. This includes all vocabulary fixed or constrained within the eCTD v4.0 XML schema.

Note: The elements in this schema are not directly referenced in this implementation guide.

7.2 eCTD v 4.0 Schema

The eCTD v4.0 schema is composed of schemas that are categorized as Interaction or Message Type. The relevant eCTD v4.0 schemas are presented in this section.

7.2.1 eCTD v 4.0 Interaction Schema

The interaction schema includes three components necessary for a complete XML message, an interaction schema, transmission wrapper schema and a control act schema. Although they are described in this section, further details will be provided in the Regional/Module 1 Implementation Guides.

7.2.1.1 *Submission Unit Sent (PORP_IN000001UV.xsd)*

This schema is to be used for all eCTD v4.0 interactions for sending submission units from the sender to the receiver. This schema indicates the message type – i.e., primary payload schema and required transmission wrappers.

7.2.1.2 *Transmission Wrapper (MCCI_MT0001000UV01.xsd)*

This schema provides the transmission wrapper, which is required for all eCTD v4.0 messages. This provides information about the sender and receiver to enable acknowledgements of the individual message.

Note: Only the required elements in this schema are mentioned in this implementation guide. Refer to Section 8.1 for required elements.

7.2.1.3 *Control Act Wrapper (MCAI_MT700201UV01.xsd)*

This schema provides the Trigger Event Control Act for the message being sent.

7.2.1.4 *Control Act (MCAI_MT900001UV01.xsd)*

This schema provides a mechanism to detect issues in the Control Act Wrapper.

7.2.2 eCTD v4.0 Payload Schema

7.2.2.1 *Payload - Message Type (PORP_MT000001UV01.xsd)*

This schema is the eCTD v4.0 base and it contains all of the elements in eCTD v4.0. This schema references many other schemas noted in the section above, including items from the Common Product Model and Common Message Element schema. The referenced schema is not described in this document, nor will they be accessed directly by implementers.

8. eCTD v4.0 XML Message

The eCTD v4.0 XML message is composed of more concepts than defined in this section of the implementation guide; this section highlights only the components that are required for Modules 2-5 of the CTD.

8.1 Message Header

The message header information provides a set of elements that are needed to specify the sender and receiver.

8.1.1 Sample XML

The following XML shows the required elements/attributes to validate the message against the schema.

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">
```

8.1.2 Required Elements

The schema requires a minimum set of information, including the following:

- ***ITSVersion*** must provide the value of "XML_1.0"
- ***xmlns*** must have the value "urn:hl7-org:v3"
- ***xmlns:xsi*** must have the value "http://www.w3.org/2001/XMLSchema-instance"
- ***xsi:schemaLocation*** must have the relative path for the current schema file "urn:hl7-org:v3../../schema/PORP_IN000001UV.xsd"[18]
- ***receiver@typeCode*** must have the value of "RCV"
- ***receiver.device@classCode*** must have a value of "DEV"
- ***receiver.device@determinerCode*** must have a value of "INSTANCE"
- ***sender@typeCode*** must have the value of "SND"
- ***sender.device@classCode*** must have a value of "DEV"
- ***sender.device@determinerCode*** must have a value of "INSTANCE"
- ***controlActProcess@classcode*** must have a value of "ACTN"
- ***conrtolActProcess@moodCode*** must have a value of "EVN"
- ***controlActProcess.subject@typecode*** must have a value of "SUBJ"

The following elements are not required by the schema, and may be required by a specific Region/Country. Refer to the Regional/Module 1 Implementation Guides for additional information about these elements:

- ***id***
- ***creationTime***
- ***interactionId***
- ***processingCode***
- ***processingModeCode***
- ***acceptAckCode***
- ***receiver.device.id***
- ***sender.device.id***

8.2 Payload Message

The following eCTD v4.0 XML message components are based on the HL7 Version 3 RPS Release 2 Normative. The information for each element is provided in discrete sections, i.e., they are not nested in the same structure of the XML Schema.

The following table provides a breakdown of the eCTD v4.0 XML structure with all elements in the XML Schema. The table is organized with the following three elements in the structure: ***submissionUnit***, ***submission*** and ***application***. The elements are annotated with balloon text boxes that provide references to either this document (highlighted in blue and referenced by Section

[18] The exact schema location will be provided in the Regional/Module 1 Implementation Guides.

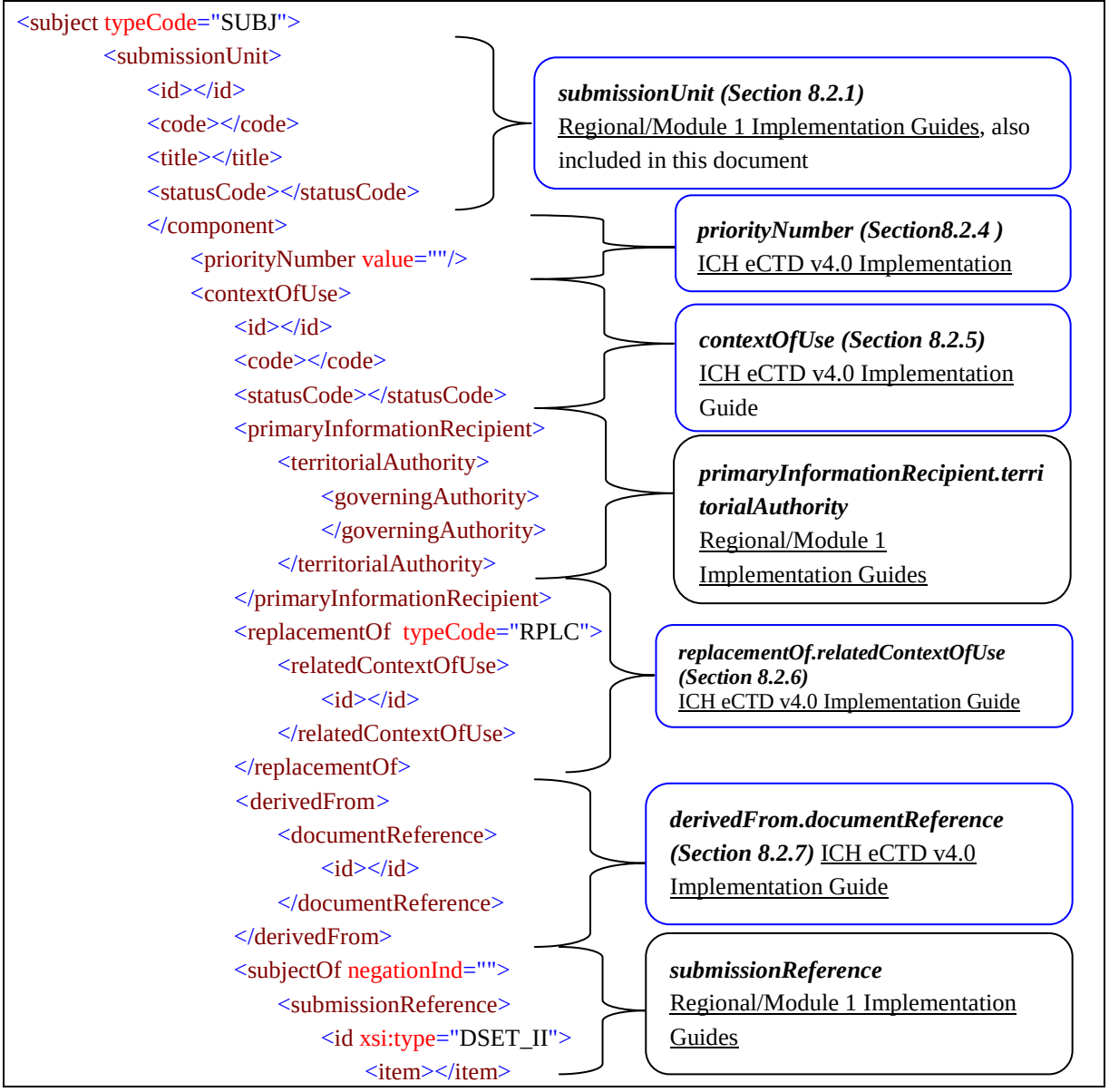
882 number) or Regional/Module 1 Implementation Guides (not highlighted and noted as Regional) to
883 identify the authoritative source of information for the element.

884 **Table 5: XML Structure**

XML Structure

The eCTD v4.0 begins by identifying the ***subject*** element of the XML message. The payload message starts with the ***submissionUnit*** element and relates the rest of the elements to the Submission Unit being sent. The ***submissionUnit*** element contains the following elements and their attributes:

- ***component.contextOfUse***
  - ***replacementOf.relatedContextOfUse***
  - ***derivedFrom.documentReference***
  - ***subjectOf.submissionReference***
  - ***referencedBy.keyword***
  - ***primaryInformationRecipient.TerritorialAuthority***
- ***componentOf1.submisison***



XML Structure

```
                    </id>
                </submissionReference>
            </subjectOf>
            <referencedBy typeCode="REFR">
                <keyword>
                    <code></code>
                </keyword>
            </referencedBy>
        </contextOfUse>
    </component>
```

Keyword (Section 8.2.8)
ICH eCTD v4.0
Implementation Guide

This section of the XML relates to specifying the ***Submission*** element. The following elements may follow the Submission: Note: All of these elements are not included in this implementation guide. Refer to the Regional/Module1 Implementation Guides for additional information.

- **sequenceNumber** (included as an element of the relationship between ***submissionUnit*** and Submission)
- **callBackContact.contactParty**
- **subject1.regulatoryStatus**
- **subject2.review**
- **subject3.regulatoryReviewTime**
- **subject4.submissionGroup**
- **subject5.mode**

XML Structure

```
<componentOf1>
    <sequenceNumber></sequenceNumber>
    <submission>
        <id></id>
        <code></code>
        <callBackContact>
            <contactParty>
                <id></id>
            </contactParty>
        </callBackContact>
        <subject2>
            <review>
                <subject1>
                    <regulatoryStatus>
                        <code></code>
                    </regulatoryStatus>
                </subject1>
            </review>
        </subject2>
        <subject3>
            <regulatoryReviewTime>
                <code></code>
            </regulatoryReviewTime>
        </subject3>
        <subject4>
            <submissionGroup>
                <id></id>
            </submissionGroup>
        </subject4>
        <subject5>
            <mode>
                <code></code>
            </mode>
        </subject5>
```

sequenceNumber.submission (Section8.2.2)

submission
Regional/Module 1 Implementation Guides

callBackContact
Regional/Module 1 Implementation Guides

review
Regional/Module 1 Implementation Guides

regulatoryStatus
Regional/Module 1 Implementation Guides

regulatoryReviewTime
Regional/Module 1 Implementation Guides

submissionGroup
Regional/Module 1 Implementation Guides

mode
Regional/Module 1 Implementation Guides

XML Structure

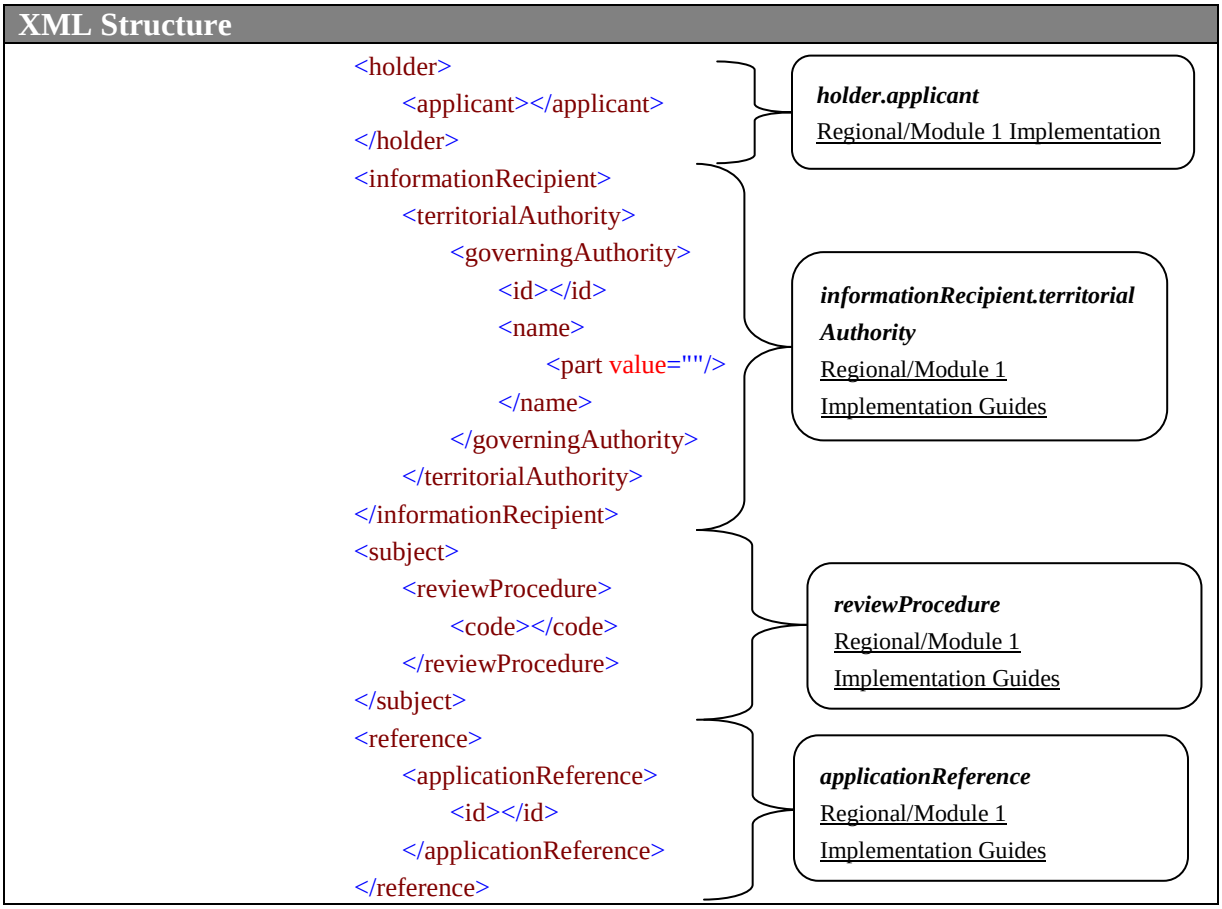
This section of the XML relates to the ***application*** element. The application section contains the following elements and their attributes:

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

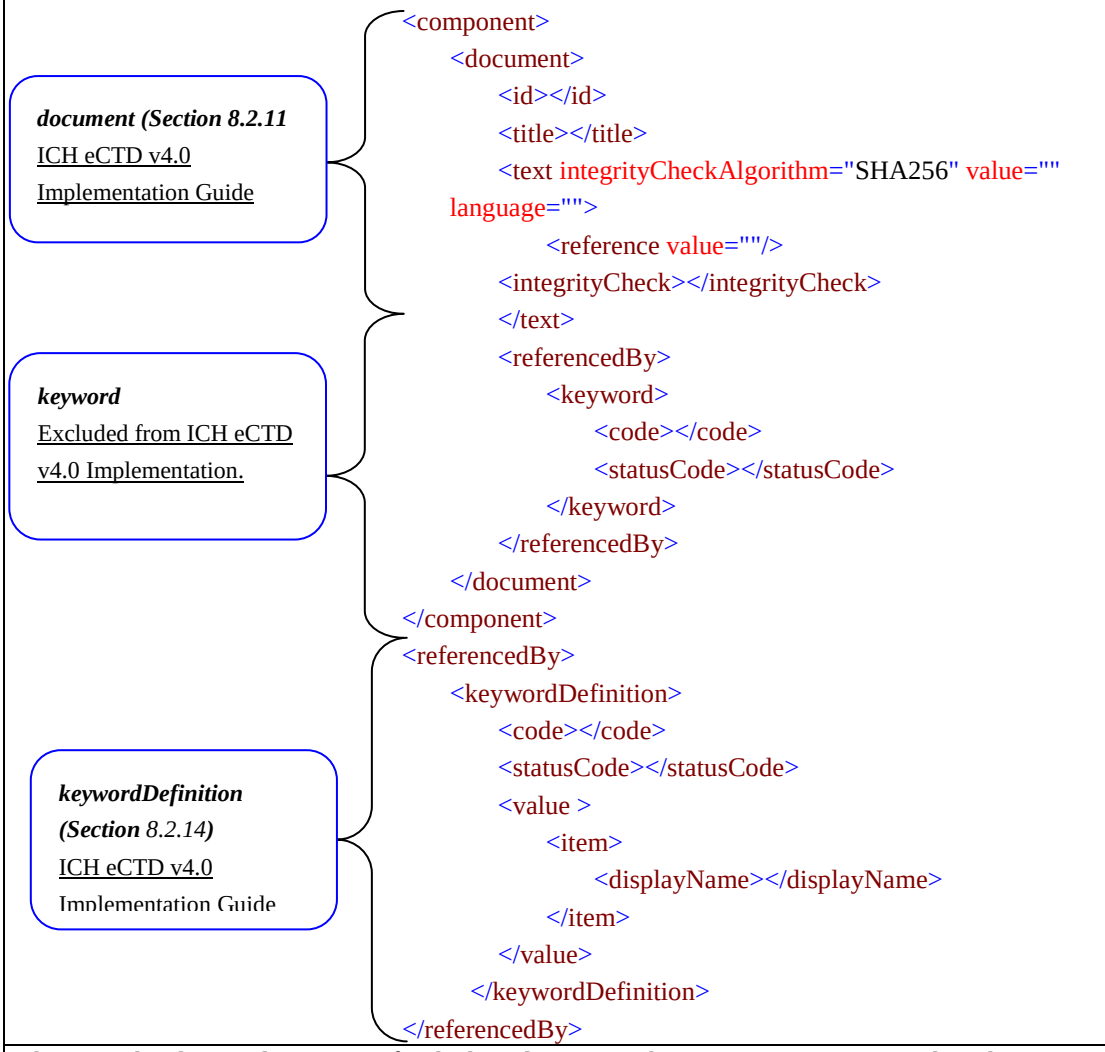
```
<componentOf>
    <application>
        <id>
            <item root="" extension=""/>
        </id>
        <code></code>
```

application (Section8.2.1 8.2.10)
Regional/Module 1 Implementation Guides, also included in this document.

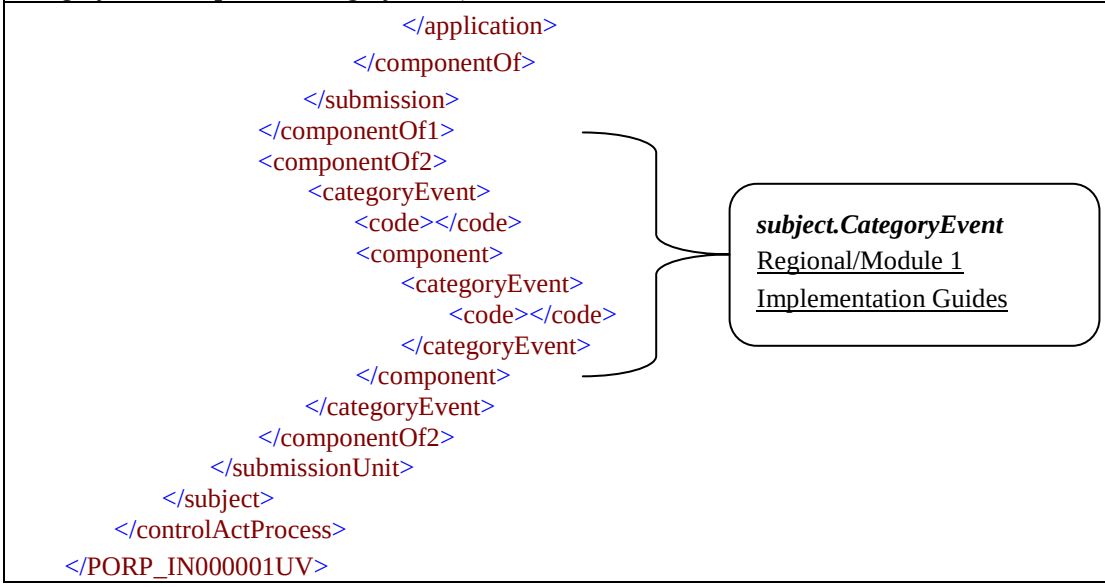
XML Structure



XML Structure



These are the closing element tags for the key elements in the eCTD v4.0 message. The submission unit's category Event is found after the closing tag for the submission, the ***componentOf2.CategoryEvent*** (and sub category with ***component.CategoryEvent***).



All information in this section is organized in order that the eCTD v4.0 XML components appear within the schema.

8.2.1 Submission Unit

The Submission Unit is a collection of documents provided to the Regulatory Authority at one time. The ***submissionUnit*** element indicates the information about an individual eCTD v4.0 XML message – i.e., only one submission unit can be sent at a time.

*Note: **submissionUnit** is primarily a Module 1 concept that will also be provided in the Regional/Module 1 Implementation Guide.*

8.2.1.1 *Location in XML*

The ***submissionUnit*** element in the XML message is in the following location:

- ***controlActProcess*** >> ***subject*** >> ***submissionUnit***

Refer to Table 5: XML Structure for the XML representation.

8.2.1.2 *XML Elements*

The following tables provide a complete set of XML elements and attributes required for the ***submissionUnit*** element, and any special instructions.

The ***classCode*** and ***moodCode*** are not required in the eCTD v4.0 XML message. The ***classCode*** is fixed to "ACT" and ***moodCode*** is fixed to "EVN". If the XML message contains any other values for these attributes it will be invalid against the schema.

Conditions that apply to the ***submissionUnit*** element:

- Only one ***SubmissionUnit*** element can exist for a message.

8.2.1.2.1 *submissionUnit.id*

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
id		[1..1]		This is the container element that uniquely identifies the submission unit sent in the message.
	root	[1..1]	Valid UUID	This is the ***root*** attribute that uniquely identifies the submission unit.
Conformance	The ***id@root*** is a required attribute.			
Business Rules	The ***id@root*** should be unique for every ***submissionUnit***.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following attributes may not be required by eCTD v4.0: • ***id@extension*** • ***id@identifierName*** • ***id@scope*** • ***id@reliability*** • ***id@displayable*** • ***id@validTimeLow*** • ***id@validTimeHigh*** • ***id@controlInformationRoot*** • ***id@controlInformationExtension*** • ***id@nullFlavor*** • ***id@flavorId*** • ***id@updateMode***			

902 8.2.1.2.2 ***submissionUnit.code***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
code		[1..1]		This is the container element for a code that will define the contents of a submission unit.
	code	[1..1]	Alpha Numeric *e.g., Original, Amendment, Presubmission*	This is the code attribute, which is a value that indicates the type of content in the ***submissionUnit*** based on regional controlled vocabulary (e.g., original).
	codeSystem	[1..1]	Valid OID	This is the ***codeSystem*** OID that is a unique identifier for the controlled vocabulary system.
Conformance	The ***code*** and ***codeSystem*** attributes are required.			
Business Rules	For ***submissionUnit*** codes consult the Regional/Module 1 Implementation Guides.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***code.displayName*** • ***code.originalText*** • ***code.translation*** • ***code.source*** • ***code@codeSystemName*** • ***code@codeSystemVersion*** • ***code@valueSet*** • ***code@valueSetVersion*** • ***code@codingRationale*** • ***code@validTimeLow*** • ***code@validTimeHigh*** • ***code@controlInformationRoot*** • ***code@controlInformationExtension*** • ***code@nullFlavor*** • ***code@flavorId*** • ***code@updateMode***			

903 8.2.1.2.3 ***submissionUnit.title***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
title		[0..1]		This is the container element for a user-specified value that describes the contents of a submission unit.
	value	[0..1]	Alpha Numeric *Sender specified description – e.g., Presubmission*	This is the ***value*** attribute of the ***title*** element, which provides a string value for the submission unit description.
Conformance	The ***title*** is an optional element.			
Business Rules	The ***title*** is a sender-specified value that describes the purpose of the submission unit.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***title.data*** • ***title.xml*** • ***title.reference*** • ***title.integrityCheck*** • ***title.thumbnail*** • ***title.description*** • ***title.translation*** • ***title@mediaType*** • ***title@charset*** • ***title@language*** • ***title@compression*** • ***title@integrityCheckAlgorithm*** • ***title@validTimeLow*** • ***title@validTimeHigh*** • ***title@controlInformationRoot*** • ***title@controlInformationExtension*** • ***title@nullFlavor*** • ***title@flavorId*** • ***title@updateMode***			

904 8.2.1.2.4 ***submissionUnit.statusCode***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
statusCode		[0..1]		This is the container element that indicates the status of the submission unit.
	code	[1..1]	Alpha Numeric *e.g., active, suspended** **Consult Regional/ Module 1 Implementation Guide*	This is the ***code*** attribute of the ***statusCode*** element, which indicates the status of the submission unit.
Conformance	If the ***statusCode*** element is provided, the ***code*** attribute is required.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	Refer to Regional/Module 1 Implementation Guides for more information about the use of ***submissionUnit.statusCode.***			
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***statusCode.part*** • ***statusCode@validTimeLow*** • ***statusCode@validTimeHigh*** • ***statusCode@controlInformationRoot*** • ***statusCode@controlInformationExtension*** • ***statusCode@nullFlavor*** • ***statusCode@flavorId*** • ***statusCode@updateMode***			

8.2.1.3 *Terminology*

All terminology will be provided as genericode files or in a spreadsheet for Step 2.[19]

8.2.1.4 *Excluded Elements*

No elements are excluded for the ***submissionUnit*** element. Refer to Regional/Module 1 Implementation Guides for more information.

8.2.2 Sequence Number

The ***sequenceNumber*** is an increasing numeric value used to maintain a sequential and chronological order within the submission or across submissions; and it is unique within an Application.

8.2.2.1 *Location in XML*

The ***sequenceNumber*** element in the XML message is in the following location:

- ***controlActProcess*** >> ***subject*** >> ***submissionUnit*** >> ***componentOf*** >> ***sequenceNumber***

There may be ***subject*** and ***component*** elements (specifically in that order) prior to the ***componentOf*** element.

Refer to Table 5: XML Structure for the XML representation.

8.2.2.2 *XML Elements*

The following table provides a complete set of XML elements and attributes required for the ***componentOf.sequenceNumber*** element, and any special instructions.

[19] Final Implementation Terminology will be provided on the ESTRI website.

The ***typeCode*** is not required in the eCTD v4.0 XML message. The ***typeCode*** is fixed to "COMP". If the XML message contains any other value for this attribute it will be invalid against the schema.

924

925 8.2.2.2.1 ***sequenceNumber***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
sequenceNumber		[1..1]		This is the container element for the sequence number and its value.
	value	[1..1]	Numeric *e.g., 1, 2, 3.*	The ***value*** attribute of the ***sequenceNumber*** element provides a whole number to be used to order Submission Unit's within a Submission element.
Conformance	***sequenceNumber@value*** attribute is required.			
Business Rules	The ***sequenceNumber*** is a positive integer. The values should begin with "1" and increment by whole numbers.			
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***sequenceNumber@controlInformationExtension*** • ***sequenceNumber@controlInformationRoot*** • ***sequenceNumber@flavorId*** • ***sequenceNumber@nullFlavor*** • ***sequenceNumber@uncertaintyType*** • ***sequenceNumber@validTimeHigh*** • ***sequenceNumber@validTimeLow*** • ***sequenceNumber.expression*** • ***sequenceNumber.originalText*** • ***sequenceNumber.uncertainty*** • ***sequenceNumber.uncertainRange***			

926

927 **8.2.2.3 *Terminology***

There is no controlled terminology for this element.

8.2.2.4 *Excluded Elements*

No elements are excluded for the ***sequenceNumber*** element.

8.2.3 XML SAMPLES: Submission Unit

The following is an example of the submission unit element and the specific attributes possible for all submission units.

```
<subject typeCode="SUBJ">
   <submissionUnit>
      <id root="0d84467e-f20b-42ad-a69a-63e61a4f7ea7"/>
       <code code="ich-amendment" codeSystem="2.16.840.1.113883.3.989.2"/>
      <title value="Original Submission for pain medication - acetyl salicylic acid tablets"/>
      <statusCode code="active"/>……
            [Additional information may appear after the statusCode (if one exists), otherwise the title or
            code elements.  For example, depending on the type of submission unit the additional
            elements may be available to select from the submission unit– subject or component
            elements]
         …
      <componentOf1>
         <sequenceNumber value="1"/>
         <submission>
            …
            [Additional information appears for the submission element.  Specific contents are defined in
            Regional/Module 1 Implementation Guide]
            …
         <componentOf>
            …
            [Additional information appears for the application element.  Specific contents are defined in
            Section 8.2.10 and Regional/Module 1 Implementation Guide]
            …
         </componentOf>
         <submission>
      </componentOf1>
      <componentOf2>
            …
            [Additional information appears for the CategoryEvent element.  Specific contents are defined
            in Regional/Module 1 Implementation Guide]
            …
      </componentOf2>
   </submissionUnit>
</subject>
```

See XML Color Legend for color usage.

Note that the ***codeSystem*** OIDS provided in the sample above are placeholders for Regional Controlled Vocabulary OIDS.

Refer to Regional/Module 1 Implementation Guides for additional information on sequence numbers, specifically when a submission unit contains more than one submission.

8.2.4 Priority Number for Context of Use

The priority number defines the order in which each Context of Use should appear within each eCTD v4.0 section of a submission unit. The ***priorityNumber*** element is always required to be provided. In cases where more than one Context of Use has the same ***contextOfUse.code*** value, the ***priorityNumber*** will be used to display the elements.

8.2.4.1 *Location in XML*

The ***priorityNumber*** element in the XML message is in the following location:

- ***controlActProcess*** >> ***subject*** >> ***submissionUnit>> component>> priorityNumber***

Refer to Table 5: XML Structure for the XML representation.

8.2.4.2 *XML Elements*

The following table provides a complete set of XML elements and attributes required for the ***component.priorityNumber*** element, and any special instructions.

The ***typeCode*** is not required in the eCTD v4.0 XML message. The ***typeCode*** is fixed to "COMP". If the XML message contains any other value for this attribute it will be invalid against the schema.

Conditions that apply to the ***priorityNumber*** element:

- If there are multiple instances of Context of Use elements with the same ***contextOfUse.code*** value the priority number will allow ordering of those elements within and across submission units for content in the same regulatory activity/submission within an application.
- If Keywords are also provided with the Context of Use, the priority number should be for the ordering of the Context of Use and Keyword combination.

8.2.4.2.1 ***priorityNumber***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
priotityNumber		[1..1]		This is the container element for the priority number and its value.

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
	value	[1..1]	Numeric *e.g., 1000,2000, 3000*	The ***value*** attribute of the ***priorityNumber*** provides a whole number to be used for ordering the Context of Use element.
	updateMode	[0..1]	Alpha *e.g., R=Replace*	The ***updateMode*** attribute provides the coded value to indicate if the ***priorityNumber*** has been changed for the Context of Use.
Conformance	***priorityNumber@value*** attribute is required.			
Business Rules	The priority number is required for each ***contextOfUse*** element. The value shall be a positive integer up to 6 digits (i.e., 1 – 999999) for the ***contextOfUse*** element with the same Context of Use code value and Keyword code value pair. It is recommended to start with "1000" and intervals of 1000 (e.g., "2000", "3000", etc.) for the initial submission of a CoU sharing the same CoU/ keyword code combination. This allows increments of one, tens and hundreds to be used when reordering and/or inserting CoU. The priority number should not be duplicated within the same CoU code and Keyword combinations. Refer to Regional/Module 1 Implementation Guides for additional business rules for priority number conflicts. The priority number will be used to order the Context of Use elements within the same CoU code and keyword combinations when displayed. If the order of the contents needs to be changed, the ***updateMode*** attribute should be used to indicate if the ***priorityNumber*** has been updated for the purposes of reordering a new CoU (i.e., ***updateMode***="R"). The ***updateMode*** should not be used unless the order of an existing Context of Use is being changed – i.e., avoid using update mode if the CoU is not being reordered with a new priority number value. Additional information is provided in Section 8.2.9.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***priorityNumber@controlInformationExtension*** • ***priorityNumber@controlInformationRoot*** • ***priorityNumber@flavorId*** • ***priorityNumber@nullFlavor*** • ***priorityNumber@uncertaintyType*** • ***priorityNumber@validTimeHigh*** • ***priorityNumber@validTimeLow*** • ***priorityNumber.expression*** • ***priorityNumber.originalText*** • ***priorityNumber.uncertainty*** • ***priorityNumber.uncertainRange***			

8.2.4.3 *Terminology*

There is no controlled terminology for this element.

8.2.4.4 *Excluded Elements*

No elements are excluded for the ***priorityNumber*** element.

8.2.5 Context of Use

8.2.5.1 *Description*

The Context of Use defines the relationship between the table of contents heading (***contextOfUse.code***) and the referenced document to be associated with that heading. The Context of Use is relevant to the sequence that it was submitted, which may include one or more ***submissions*** referenced in the ***submissionUnit***.

The Context of Use code and reference to a document (i.e., ***documentReference***) will be used to connect the content of the submission unit to one or more uses in a table of contents.

*The **contextOfUse** element will be repeated as necessary for a submission unit – i.e., there may be many **contextOfUse** elements in an XML message.*

*For each **contextOfUse** element a **priorityNumber** should always be specified to indicate the order in which the Context of Use should be displayed. The **priorityNumber** will be used to order the **contextOfUse** elements that are submitted with the same **contextOfUse.code*** and ***keyword.code***.

8.2.5.2 *Location in XML*

The ***contextOfUse*** element in the XML message is in the following location:

- ***controlActProcess***>> ***subject***>> ***submissionUnit>>component>>priorityNumber>*** ***contextOfUse***

Refer to Table 5: XML Structure for the XML representation.

8.2.5.3 *XML Elements*

The following tables provide a complete set of XML elements and attributes required for the ***contextOfUse*** element, and any special instructions.

The ***classCode*** and ***moodCode*** are not required in the eCTD v4.0 XML message. The ***classCode*** is fixed to "DOC" and ***moodCode*** is fixed to "EVN". If the XML message contains any other values for these attributes it will be invalid against the schema.

Conditions that apply to the ***contextOfUse*** element:

- Zero to many ***contextOfUse*** elements can be sent in a ***submissionUnit.***

8.2.5.3.1 *contextOfUse.id*

Element	Attribute	Cardinality	Value(s) Allowed	Description *Instructions*
id		[1..1]		This is the container element that organizes the ***contextOfUse*** identifier.
	root	[1..1]	Valid UUID	The ***root*** attribute of the ***id*** element provides a global unique identifier of the ***contextOfUse.***
Conformance	***id@root*** is a required attribute.			
Business Rules	The ***id@root*** should be unique for every ***contextOfUse*** submitted.			

Element	Attribute	Cardinality	Value(s) Allowed	Description *Instructions*
Excluded Elements and/or Attributes	The following attributes may not be required by eCTD v4.0: • ***id@extension*** • ***id.item@identifierName*** • ***id.item@scope*** • ***id.item@reliability*** • ***id.item@displayable*** • ***id@validTimeLow*** • ***id@validTimeHigh*** • ***id@controlInformationRoot*** • ***id@controlInformationExtension*** • ***id@nullFlavor*** • ***id@flavorId*** • ***id@updateMode***			

1012 8.2.5.3.2 ***contextOfUse.code***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
code		[0..1]		This is the container element for the type of content referenced under the ***contextOfUse***.
	code	[1..1]	Alpha Numeric	The ***code*** attribute provides a coded value that indicates the heading and is defined by ICH or Regulatory Authorities.
	codeSystem	[1..1]	Valid OID	The ***codeSystem*** attribute provides a unique identifier that indicates the controlled vocabulary system. *This should be the OID registered for the code system.*
Conformance	If the ***code*** element is provided, the ***code*** and ***codeSystem*** attributes must be provided.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	The ***code*** element is required when sending the Context of Use. The ***code*** element is not required if the ***contextOfUse.statusCode*** is inactivated (i.e., status code equals suspended).			
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***code.displayName*** • ***code.originalText*** • ***code.translation*** • ***code.source*** • ***code@codeSystemName*** • ***code@codeSystemVersion*** • ***code@valueSet*** • ***code@valueSetVersion*** • ***code@codingRationale*** • ***code@validTimeLow*** • ***code@validTimeHigh*** • ***code@controlInformationRoot*** • ***code@controlInformationExtension*** • ***code@nullFlavor*** • ***code@flavorId*** • ***code@updateMode***			

1013

1014 8.2.5.3.3 ***contextOfUse.statusCode***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
statusCode		[1..1]		This is the container element that has a controlled terminology code that indicates the status of the Context of Use.

	code	[1..1]	Alpha *e.g., active, suspended** **Refer to Regional/Module 1 Implementation Guide*	The ***code*** attribute provides a specified value that indicates whether the Context of Use is still relevant or if it has been removed.
Conformance	The ***statusCode*** element is always required when a CoU is specified.			
Business Rules	The ***statusCode@code*** must always be sent in the message.			
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***statusCode.part*** • ***statusCode@validTimeLow*** • ***statusCode@validTimeHigh*** • ***statusCode@controlInformationRoot*** • ***statusCode@controlInformationExtension*** • ***statusCode@nullFlavor*** • ***statusCode@flavorId*** • ***statusCode@updateMode***			

8.2.5.4 *Terminology*

All terminology will be provided as genericode files or in a spreadsheet for Step 2.[20]

ICH Codes may be further constrained by regulatory authorities, consult the appropriate Regional/Module 1 Implementation Guide.

8.2.5.5 *Excluded Elements*

No elements are excluded for the ***contextOfUse*** element.

8.2.6 Related Context of Use (Context of Use Life Cycle)

The ***relatedContextOfUse*** element allows the sender to relate a ***contextOfUse*** element to one or more ***relatedContextOfUse*** elements. The ***replacementOf*** relationship is used for tracking the life cycle of context of use elements.

8.2.6.1 *Location in XML*

The ***relatedContextOfUse*** element in the XML message is in the following location:

[20] Final Implementation Terminology will be provided on the ESTRI website.

- ***controlActProcess***>> ***subject***>> ***submissionUnit>>component>>priorityNumber>*** ***contextOfUse>> replacementOf>> relatedContextOfUse***

Refer to Table 5: XML Structure for the XML representation.

8.2.6.2 *XML Elements*

The following table provides a complete set of XML elements and attributes required for the ***relatedContextOfUse*** element, and any special instructions.

The ***classCode*** and ***moodCode*** are not required in the eCTD v4.0 XML message. The ***classCode*** is fixed to "DOC" and ***moodCode*** is fixed to "EVN". If the XML message contains any other values for these attributes it will be invalid against the schema.

Conditions that apply to the ***relatedContextOfUse*** element:

- One or more ***relatedContextOfUse*** elements may be provided in the XML as being replaced by the new ***contextOfUse.***

8.2.6.2.1 *relatedContextOfUse.id*

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
id		[1..1]		This is the container element for a related contextOfUse as referenced by an identifier.
	root	[1..1]	Valid UUID	This is the ***root*** attribute of the ***id*** element that provides the global unique identifier for the ***relatedContextOfUse*** element being replaced.
Conformance	The ***id@root*** is a required attribute			
Business Rules	One ***contextOfUse*** element can include one or more ***relatedContextOfUse*** elements.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following attributes may not be required by eCTD v4.0: • ***id@extension*** • ***id@identifierName*** • ***id@scope*** • ***id@reliability*** • ***id@displayable*** • ***id@validTimeLow*** • ***id@validTimeHigh*** • ***id@controlInformationRoot*** • ***id@controlInformationExtension*** • ***id@nullFlavor*** • ***id@flavorId*** • ***id@updateMode***			

8.2.6.3 *Terminology*

All terminology will be provided as genericode files or in a spreadsheet for Step 2.[21]

8.2.6.1 *Excluded Elements*

No elements are excluded for the ***relatedContextOfUse*** element.

8.2.7 Document Reference

Since a document can be used multiple times, a ***documentReference*** element allows a document to be specified for the ***contextOfUse***. Each time the document is used in the same submission unit, that document may have a different ***contextOfUse***. Accordingly, each Context of Use must reference a document.

8.2.7.1 *Location in XML*

The ***documentReference*** element in the XML message is in the following location:

- ***controlActProcess***>> ***subject***>> ***submissionUnit>>component>>priorityNumber>*** ***contextOfUse>> derivedFrom>> documentReference***

There may be one or more ***replacementOf*** elements prior to the ***derivedFrom*** element.

Refer to Table 5: XML Structure for the XML representation.

8.2.7.2 *XML Elements*

The following table provides a complete set of XML elements and attributes required for the ***documentReference*** element, and any special instructions.

[21] Final Implementation Terminology will be provided on the ESTRI website.

The ***classCode*** and ***moodCode*** are not required in the eCTD v4.0 XML message. The ***classCode*** is fixed to "DOC" and ***moodCode*** is fixed to "EVN". If the XML message contains any other values for these elements it will be invalid against the schema.

Conditions that apply to the ***documentReference*** element:

- Zero to one ***documentReference*** elements can be sent for each ***contextOfUse.***
- For a contextOfUse.statusCode= active – the ***documentReference*** element is required.
- For a contextOfUse.statusCode= suspended – the ***documentReference*** element should not be provided.

8.2.7.2.1 *documentReference.id*

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
id		[1..1]		This is the container element for a reference to a Document.
	root	[1..1]	Valid UUID	The ***root*** attribute or the ***id*** element provides a global unique identifier of the Document being referenced.
Conformance	The ***id@root*** attribute is required if the ***documentReference*** element is provided.			
Business Rules	The ***id@root*** is a reference to a document sent in the submission unit or a previously submitted submission unit. *Note: Refer to applicable Regional/Module 1 Implementation Guide for specifics on document retention of regulatory submissions.*			
Excluded Elements and/or Attributes	The following attributes may not be required by eCTD v4.0: • ***id@extension*** • ***id@identifierName*** • ***id@scope*** • ***id@reliability*** • ***id@displayable*** • ***id@validTimeLow*** • ***id@validTimeHigh*** • ***id@controlInformationRoot*** • ***id@controlInformationExtension*** • ***id@nullFlavor*** • ***id@flavorId*** • ***id@updateMode***			

8.2.7.3 *Terminology*

There is no controlled terminology for this element.

8.2.7.4 *Excluded Elements*

No elements are excluded for the ***documentReference*** element.

8.2.8 Keyword

The ***keyword*** element is used for the purposes of transmitting additional information about a ***contextOfUse***. The ***keyword*** is either defined by an external controlled vocabulary or it may be defined within the message as ***keywordDefinition***.

8.2.8.1 *Location in XML*

The ***keyword*** element in the XML message is in the following location for Context of Use:

- ***controlActProcess***>> ***subject***>> ***submissionUnit>>component>>priorityNumber>*** ***contextOfUse>> referencedBy>> keyword***

There may be a ***primaryInformationRecipient***, ***replacementOf***, ***derivedFrom***, or ***subjectOf*** element prior to the ***referencedBy*** element.

Refer to Table 5: XML Structure for the XML representation. Note: document keyword elements are excluded in eCTD v4.0 messages.

8.2.8.2 *XML Elements*

The following table provides a complete set of XML elements and attributes required for the ***keyword*** element, and any special instructions.

The ***classCode*** and ***moodCode*** are not required in the eCTD v4.0 XML message. The ***classCode*** is fixed to "ACT" and ***moodCode*** is fixed to "EVN". If the XML message contains any other values for these attributes it will be invalid against the schema.

The ***typeCode*** is required in the eCTD v4.0 XML message. The ***typeCode*** should be to "REFR". If the XML message contains any other value for this attribute it will be invalid against the schema.

Conditions that apply to the ***keyword*** element:

- Zero to many ***keyword*** elements can be sent for each ***contextOfUse*** element.
- Consult Regional/Module 1 Implementation Guides for specific types of Keywords that should be used with ***contextOfUse*** elements.

1085 8.2.8.2.1 ***keyword.code***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Code		[1..1]		This is the container element that identifies the keyword.
	code	[1..1]	Alpha Numeric *e.g., "M123456" for Manufacture Site*	This is the ***code*** attribute that identifies the code value for the keyword.
	codeSystem	[1..1]	Valid OID	This is the ***codeSystem*** OID that is a unique identifier for the controlled vocabulary system. *This should be the OID registered for the code system.*
Conformance	The ***code*** and ***codeSystem*** attributes are required. A keyword can only have one code.			
Business Rules	The display name for the ***code*** needs to be retrieved from the corresponding code system.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***code.displayName*** • ***code.originalText*** • ***code.translation*** • ***code.source*** • ***code@codeSystemName*** • ***code@codeSystemVersion*** • ***code@valueSet*** • ***code@valueSetVersion*** • ***code@codingRationale*** • ***code@validTimeLow*** • ***code@validTimeHigh*** • ***code@controlInformationRoot*** • ***code@controlInformationExtension*** • ***code@nullFlavor*** • ***code@flavorId*** • ***code@updateMode***			

8.2.8.3 *Terminology*

All terminology will be provided as genericode files or in a spreadsheet for Step 2.[22]

8.2.8.4 *Excluded Elements*

No elements are excluded for the ***keyword*** element.

8.2.9 XML SAMPLES: Context of Use

8.2.9.1 *Context of Use Elements / Context of Use Keywords*

The following is an example of the XML for the Context of Use. The ***contextOfUse*** enters as a ***component*** of the ***submissionUnit*** element. Each component is required to include on priority number element.

```
<component>
    <priorityNumber value="1000"/>
    <contextOfUse>
        <id root="1f080afd-f5d4-4cec-8d09-2bf0ea6bec66"/>
        <code code="ich-3-2-s-2-3" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
        <statusCode code="active"/>
            …
            [Additional information may appear after the addition of the contextOfUse –
            primaryInformationRecipient]
```

[22] Final Implementation Terminology will be provided on the ESTRI website.

```
                …
            <replacementOf typeCode=“RPLC”>
                <relatedContextOfUse>
                    <id root=“25fdfdcb-a2a2-4f2b-a2aa-9ccb4c096acb”/>
                </relatedContextOfUse>
            </replacementOf >
            <derivedFrom>
                <documentReference>
                    <id root=“8dc27e78-41ef-4b8d-960d-2626b743f194”/>
                </documentReference>
            </derivedFrom>
                …
                [Additional information may appear after the addition of the
                subjectOf.submissionReference,]
                …
            <referencedBy typeCode="REFR">
                <keyword>
                    <code code=“ich-species-4”codeSystem=“2.16.840.1.113883.3.989.2.2.4.1.4”/>
                </keyword>
            </referencedBy>
        </contextOfUse>
    </component>
```

See XML Color Legend for color usage.

The Context of Use element can be ordered by using the priority number to show the order in which the Context of Use elements should be displayed when they have the same ***ContextOfUse.code*** and ***keyword***. The XML Sample below depicts an example of how both priority number and keywords are used in relation to the Context of Use.

```
<component>
<priorityNumber value="1000"/>
    <contextOfUse>
        <id root="27c069e1-8fec-4b07-907e-cf691543cf66"/>
        <code code="ich-3-2-s-2-3" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
        <statusCode code="active"/>
        <derivedFrom>
        <!--Document titled “Controls for Material YYY”-->
            <documentReference>
                <id root="26a7e20a-b7b6-4729-adcf-75fb90097d68"/>
            </documentReference>
        </derivedFrom>
        <referencedBy typeCode="REFR">
            <keyword>
                <code code="MANU001" codeSystem="2.16.840.1.113883.X"/>
            </keyword>
```

```
            </referencedBy>
            <referencedBy typeCode="REFR">
                <keyword>
                    <code code="SUB001" codeSystem="2.16.840.1.113883.X"/>
                </keyword>
            </referencedBy>
        </contextOfUse>
    </component>
    <component>
    <priorityNumber value="2000"/>
        <contextOfUse>
            <id root="749e6f91-797b-4aeb-89c6-7cf7b9402c15"/>
            <code code="ich-3-2-s-2-3" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
            <statusCode code="active"/>
            <derivedFrom>
            <!--Document titled “Analytical Method #234”-->
                <documentReference>
                        <id root="57e00a6f-5425-4c0e-98ad-ca4b2e0befea"/>
                </documentReference>
            </derivedFrom>
            <referencedBy typeCode="REFR">
                <keyword>
                    <code code="MANU001" codeSystem="2.16.840.1.113883.X"/>
                </keyword>
            </referencedBy>
            <referencedBy typeCode="REFR">
                <keyword>
                    <code code="SUB001" codeSystem="2.16.840.1.113883.X"/>
                </keyword>
            </referencedBy>
        </contextOfUse>
    </component>
```

8.2.9.2 *Managing Context of Use Elements*

The life cycle management of a ***contextOfUse*** is covered in this section. Once a ***contextOfUse*** is submitted with its id it starts the life cycle for that ***contextOfUse***. The following rules have been harmonized:

- When replacing a Context of Use, the two instances must have the same ***contextOfUse.code*** and associated Keywords (i.e., this will allow it to appear in exactly the same table of contents location when it is replaced).
- The replacement of Context of Use will make the previous ***contextOfUse*** element obsolete (i.e., the ***relatedContextOfUse*** element(s)).

The following are reasons for changes to the ***contextOfUse*** through its life cycle:

- **New Version:** To version a ***contextOfUse***, a different document will need to be indicated in the ***documentReference*** element.

- **Removal (Inactivation) of Context of Use:** If the Context of Use needs to be removed at any time during the life cycle of the submission, a submission unit may indicate the removal of the Context of Use by changing the ***statusCode*** element.

8.2.9.2.1 *Inserting New Context of Use Elements*

If a ***submissionUnit*** includes components with the same ***contextOfUse*** code and ***keyword*** code, a priority should be set on the ***component*** to specify the relative display position of the ***contextOfUse*** relative to the other ***contextOfUse*** elements.

```
<component>
<priorityNumber value="1000"/>
    <contextOfUse>
        <id root="fd28ce84-651a-437f-b7f0-5171ad21057d"/>
        <code code="ich-3-3" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
        <statusCode code="active"/>
        <derivedFrom>
        <!-- Literature Reference Document #1-->
            <documentReference>
                <id root="0ac0295e-766f-4567-9d63-40b8180de0c0"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
<component>
<priorityNumber value="2000"/>
    <contextOfUse>
        <id root="d27a4269-eebc-449f-9f33-645907f964984"/>
        <code code="ich-3-3" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
        <statusCode code="active"/>
        <derivedFrom>
        <!--Literature Reference Document #2-->
            <documentReference>
                <id root="839235d5-1409-46c6-a144-e4fc3988e313"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

In subsequent submission units of a submission (i.e., regulatory activity) or application, it may be necessary to add a Context of Use with the same ***contextOfUse.code*** as a previous sequence.

The following example adds a new Context of Use with the same ***contextOfUse.code*** and keywords as in the previous examples. This Context of Use will appear between the two previously provided Context of Use elements.

Inserting Context of Use

```
<component>
<priorityNumber value="1500"/>
    <contextOfUse>
        <id root="d5528cfc-15f8-479e-ab59-562c0aa3a5d8"/>
        <code code="ich-3-2-s-2-3" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
        <statusCode code="active"/>
        <derivedFrom>
            <!—Literature Reference Document #3-->
            <documentReference>
                <id root="1982f2bf-bd82-45c6-83d7-8838598c971f"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

8.2.9.2.2 *Reordering Context of Use*

There will be times when the ***contextOfUse*** elements may be sent in the incorrect order for display and the sender wants to correct the order.

Reordering may also need to occur when a new Context of Use needs to be inserted between existing CoU (see Section 8.5.3 for additional information). When the ***contextOfUse*** elements need to be reordered, the following basic rules should be followed:

- If a new component is added during the reordering, that ***contextOfUse*** element does not use the ***contextOfUse.priorityNumber@updateMode*** attribute.
- The ***contextOfUse.priorityNumber@updateMode*** is used for the component being renumbered

The following example is the basic reordering of the previous context of use that was sent in the incorrect order. Note: the sender should never or rarely send a submission unit just to reorder ***contextOfUse*** elements. The previous Context of Use with a priority number of 1000 does not need to be sent again in this submission unit.

The following example shows the reordering of a previously submitted Context of Use (note that only the required elements and attributes are sent) to have a placement prior to the Context of Use with priority number of 1000.

Reordering a Context of Use

```
<component>
<priorityNumber value="900" updateMode="R"/>
    <contextOfUse>
        <id root="d5528cfc-15f8-479e-ab59-562c0aa3a5d8"/>
        <statusCode code="active"/>
    </contextOfUse>
</component>
```

Note: the example above does not address the keywords that may be applied to the Context of Use. For the purposes of the example above, the assumption shows that the Context of Use does not include keywords.

8.2.9.2.3 *Removing / Inactivating Context of Use Elements*

In subsequent submission units, it may be necessary to remove an existing Context of Use (i.e., it is not being replaced by another Context of Use). In this case, the Context of Use will no longer be displayed as active.

Removing a Context of Use

```
<component>
<priorityNumber value="900"/>
    <contextOfUse>
        <id root="d5528cfc-15f8-479e-ab59-562c0aa3a5d8"/>
        <statusCode code="suspended"/>
    </contextOfUse>
</component>
```

8.2.9.2.4 *Replacing (Versioning) Context of Use Elements*

In subsequent submission units of a submission (i.e., regulatory activity), it may be necessary to replace a ***contextOfUse*** element within a new ***contextOfUse*** element. There are two reasons for submitting a replacement:

1. The submission contents (i.e., the document being referenced) have changed
2. The previous inactive submission content need to be reinstated as active.

The new ***contextOfUse*** element will have a new unique identifier and all of the corresponding attributes. In addition, a ***relatedContextOfUse*** element is used to identify the Context of Use being replaced. This is a simple relationship and does not include anything but a reference of the unique identifier of the ***relatedContextOfUse***. The ***priorityNumber*** of the element should be used to place content in the correct order based on the desired placement among previously submitted submission content.

```
<component>
<priorityNumber value="1000"/>
    <contextOfUse>
        <id root="b205bb7c-a222-4557-a954-0363dc122ca8"/>
        <code code="ich-2-7-1" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1" />
        <statusCode code="active"/>
        <replacementOf typeCode="RPLC">
            <relatedContextOfUse>
                <id root="78b2f721-25f0-474d-914b-5efb026cc7f7"/>
            </relatedContextOfUse>
        </replacementOf>
        <derivedFrom>
        <!--Document-->
            <documentReference>
                <id root="6ee97feb-8cd1-4991-8c38-002f16102fca"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

8.2.10 Application

The Application element is presented in this section of the Implementation Guide as it is the connection point for the ***document*** and ***keywordDefinition*** elements in the XML message. The concept of Application element differs among regions.

Note: Application is primarily a Module 1 concept that will also be described in the Regional/Module 1 Implementation Guide.

8.2.10.1 *Location in XML*

The ***application*** element in the XML message is in the following location for documents:

- ***controlActProcess***>> ***subject***>> ***submissionUnit***>>***componentOf***>>***submission***>> ***componentOf***>>***application***

Refer to Table 5: XML Structure for the XML representation.

8.2.10.2 *XML details*

The following is an example of the XML for the application information. The application enters as a ***componentOf*** element between ***submission*** and ***application***.

```
…
[This XML section will repeat for each application element. A submission element is a componentOf an
application element]
…
<componentOf>
    <application>
        <id>
```

```
            <item root="f23c558f-cd58-41bc-bf6f-c6d230d3d665" extension="987654"/>
        …
        <!--Additional item elements can be added here-->
        …
        </id>
        <code code="C72899" codeSystem="2.16.840.1.113883.3.26.1.1"/>
            …
            [Additional information may appear after the addition of the application.code, for
            example any of the following elements related to application – component,
            referencedBy, informationRecipient, reference, subject, or holder]
            …
    </application>
</componentOf>
```

See XML Color Legend for color usage

8.2.10.3 *XML Elements*

The following tables provide a complete set of XML elements and attributes required for the ***application*** element, and any special instructions.

The ***classCode*** and ***moodCode*** are not required in the eCTD v4.0 XML message. The ***classCode*** is fixed to "ACT" and ***moodCode*** is fixed to "EVN". If the XML message contains any other values for these attributes it will be invalid against the schema.

8.2.10.3.1 ***application.id***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
id		[1..1]		This is the container element of the following elements and attributes by which it uniquely identifies the application.

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
id.item		[1..*]		This is the container element of the following attributes by which it uniquely identifies the application, because an application can be given multiple identifiers across territories, one ***id.item*** element should be used for each unique application identifier.
	root	[1..1]	Valid UUID	The ***root*** attribute of the ***id*** element provides a global unique identifier.
	extension	[0..1]	Alpha Numeric *e.g., 123456 (U.S. NDA value)*	The ***extension*** attribute of the ***id*** element provides a location to specify a region-specific application tracking number.
Conformance	The ***id.item@root*** attribute is required for the ***application*** element.			
Business Rules	The ***id.item@root*** attribute should stay the same for an ***id.item@extension*** value through the entire life cycle of the regulatory activity. The ***id.item*** element may be repeated as many times as necessary to indicate one to many application identifier values. Refer to Regional/Module 1 Implementation Guide for assignment of application number.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following attributes may not be required by eCTD v4.0: • ***id.item@identifierName*** • ***id.item@scope*** • ***id.item@reliability*** • ***id.item@displayable*** • ***id@validTimeLow*** • ***id@validTimeHigh*** • ***id@controlInformationRoot*** • ***id@controlInformationExtension*** • ***id@nullFlavor*** • ***id@flavorId*** • ***id@updateMode***			

1360 8.2.10.3.2 ***application.code***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
code		[1..1]		This is the container element that organizes the coded value for the application.
	code	[1..1]	Alpha Numeric *Terminology is specified by the appropriate Regional/ Module 1 Implementation Guide*.	The ***code*** attribute is a unique value that indicates the type of content in the application based on regional controlled vocabulary (e.g., NDA, MAA, Art-8-3, Art-10-1, etc.).
	codeSystem	[1..1]	Valid OID	The ***codeSystem*** attribute is a unique identifier that indicates the controlled vocabulary system. *This should be the OID registered for the code system.*
Conformance	There must be one and only one ***code@code*** attribute specified for an application.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	Refer to Regional/Module 1 Implementation Guide for additional information.			
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***code.displayName*** • ***code.originalText*** • ***code.translation*** • ***code.source*** • ***code@codeSystemName*** • ***code@codeSystemVersion*** • ***code@valueSet*** • ***code@valueSetVersion*** • ***code@codingRationale*** • ***code@validTimeLow*** • ***code@validTimeHigh*** • ***code@controlInformationRoot*** • ***code@controlInformationExtension*** • ***code@nullFlavor*** • ***code@flavorId*** • ***code@updateMode***			

8.2.10.4 *Terminology*

All terminology will be provided as genericode files or in a spreadsheet for Step 2.[23]

Refer to the appropriate Regional/Module 1 Implementation Guide for region-specific information for application type codes.

8.2.10.5 *Excluded Elements*

No elements are excluded for the Application element. Refer to Regional/Module 1 Implementation Guides for more information.

8.2.11 Document

The ***document*** element is used for the purposes of transmitting the information about each document related to an application. Documents (e.g., PDF files) are prepared by the Applicant for review by the Regulatory Authority. A document may change over time. One document can be associated with multiple ***contextOfUse*** elements, and may be used in multiple submission units.

The initial transmission of a document and its complete set of document elements/attributes are considered the creation of a document. Once the document has been identified to the receiving

[23] Final Implementation Terminology will be provided on the ESTRI website.

system, it can be referenced by its identifier in future uses of the document. The existing document title must apply in the new use.

8.2.11.1 *Location in XML*

The ***document*** element in the XML message is in the following location for documents:

- ***controlActProcess***>> ***subject***>> ***submissionUnit>>componentOf>>submission>> componentOf>>application>> component > document***

There may be ***holder***, ***subject***, or ***reference*** element prior to the ***component*** element.

Refer to Table 5: XML Structure for the XML representation.

8.2.11.2 *XML Elements*

The following tables provide a complete set of XML elements and attributes required for the ***document*** element, and any special instructions.

The ***classCode*** and ***moodCode*** are not required in the eCTD v4.0 XML message. The ***classCode*** is fixed to "DOC" and ***moodCode*** is fixed to "EVN". If the XML message contains any other values for these attributes it will be invalid against the schema.

Conditions that apply to the ***document*** element:

- One or more ***document*** elements may follow the ***application*** element

8.2.11.2.1 *document.id*

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
id		[1..1]		This is the container element for the document identifier.
	root	[1..1]	Valid UUID	This ***root*** attribute of the ***id*** element is a global unique identifier of the ***document.***
Conformance	The ***root*** is a required attribute.			
Business Rules	The ***id@root*** should be unique for every ***document*** element, i.e., there should not be two documents submitted with the same ***id@root*** value.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following attributes may not be required by eCTD v4.0: • ***id@extension*** • ***id@identifierName*** • ***id@scope*** • ***id@reliability*** • ***id@displayable*** • ***id@validTimeLow*** • ***id@validTimeHigh*** • ***id@controlInformationRoot*** • ***id@controlInformationExtension*** • ***id@nullFlavor*** • ***id@flavorId*** • ***id@updateMode***			

1387 8.2.11.2.2 ***document.title***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
title		[1..1]		This is the container for the ***title*** element of a document.
	value	[1..1]	Alpha Numeric and/or Japanese characters Sender-specified title *e.g., "General Information"*	This is the ***value*** attribute of the ***title*** element provides the title for the document. *This is a sender-specified value for each document.*
	updateMode	[0..1]	Alpha *E.g., R= Replace*	The ***updateMode*** attribute that is used if updating the ***document.title*** element.
Conformance	The ***title@value*** attribute is required for all documents.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	The ***title*** element should be used to indicate a human-readable value when displaying the document file. When sending a change in the ***title*** element, the ***title@updateMode*** attribute should be provided with only a value of "R". The ***updateMode*** should not be used unless the order of an existing Document title is being changed – i.e., avoid using ***updateMode*** if the title value is the same. Refer to Section 8.2.14.3.2 for information about updating ***document.title.***			
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***title.translation*** • ***title@validTimeLow*** • ***title@validTimeHigh*** • ***title@controlInformationRoot*** • ***title@controlInformationExtension*** • ***title@nullFlavor*** • ***title@flavorId*** • ***title@language***			

1388 8.2.11.2.3 ***document.text***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
text		[0..1]		This is the container element that provides additional information about the document.
	integrityCheckAlgorithm	[1..1]	Alpha Numeric *e.g., SHA256*	This is the type of ***integrityCheckAlgorithm*** that was used for the checksum values provided in ***integrityCheck*** element.

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
	language	[0..1]	Alpha *Refer to ISO 639.1 for two-letter language codes* *Refer to Regional/Module 1 Implementation Guide*	This is the ***language*** attribute to indicate the language for the document.
	mediaType	[0..1]	Alpha Numeric *Refer to Regional/Module 1 Implementation Guide*	This is the ***mediaType*** attribute that specifies the usage of the file where it is regionally requested.
text.reference		[0..1]		This is the container element within the ***text*** element for a document.
	value	[1..1]	Alpha Numeric File path of the document *e.g., "../m3/32-body-data/32s-drug-sub/32s1-gen-info.pdf"*	This is the ***value*** attribute of the ***text*** element that provides the location of the document with the relative path and filename of the document.
text.integrityCheck		[1..1]	Alpha Numeric *e.g., "618102bf07065bcc1250594201fe448515f0fa61"*	This is the integrity check element, which has the checksum value.
Conformance	Documents require the following elements/attributes: • The ***text*** element o The ***text@IntegrityCheckAlgorithm*** attribute o The ***reference@value*** attribute o The ***text.integrityCheck*** element			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	The ***text*** element should be used when sending a document. The ***text@language*** and ***text@mediaType*** attributes are optional. Refer to Regional/Module 1 Implementation Guides for additional information. For file reuse, the ***text*** element must indicate the same ***reference@value***, ***text@IntegrityCheckAlgorithm*** and ***text.integrityCheck*** values of the previously submitted ***document*** element.			
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***text.xml*** • ***text.data*** • ***text.description*** • ***text.thumbnail*** • ***text.translation*** • ***text@charset*** • ***text@compressiontext@translation*** • ***text@validTimeLow*** • ***text@validTimeHigh*** • ***text@controlInformationRoot*** • ***text@controlInformationExtension*** • ***text@nullFlavor*** • ***text@flavorId***			

8.2.11.3 *Terminology*

There is no controlled terminology for this element.

8.2.11.4 *Excluded Elements*

No elements are excluded for the ***document*** element.

8.2.12 Document Keyword

All Keywords are applied to the Context of Use – i.e., eCTD v4.0 does not allow document keywords.

8.2.13 XML SAMPLES: Application/Document

The following XML Samples build the ***document*** element as specified for an Application.

8.2.13.1 *Documents*

The following is an example of a document.

```
<document>
```

```
    <id root="973d9293-77b9-4f45-b62e-aae62d7ce814"/>
    <title value="Process and Controls"/>
    <text integrityCheckAlgorithm="SHA256">
        <reference value="../m3/32-prod/manuf-process-and-controls.pdf"/>
        <integrityCheck>c0d5623550c997a70b62717d95fca1cada201754d1ed9fbbbbfa97bfd64c8ea4
    </integrityCheck>
    </text>
</document>
```

8.2.14 Approaches to Changes in Document Groups

This section describes the management of ***ContextOfUse*** elements as document groups consisting of one or more context of use elements that change over time. The following section provides information about using keywords to group one or more Context elements together as well as changes in content composition.

8.2.14.1 *Use of Keywords for Group Title*

The submitter may use a keyword to add a group title to the Context of Use to further organize content under a table of contents heading.

```
                <component>
                <priorityNumber value="1000"/>
                    <contextOfUse>
                        <id root="1f271446-8d56-4ddc-b730-eaee208c7053"/>
                        <code code="ich-3-2-p-7" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
                        <statusCode code="active"/>
                        <!--Document Referenced is Analytical Procedure 1-->
                        <derivedFrom>
                            <documentReference>
                                <id root="164af1e4-f625-4621-8d69-ca56b8f7dc7b"/>
                            </documentReference>
                        </derivedFrom>
                        <!--C001 is the code for the Group Title Keyword Definition "PVDC Bilster
Pack"-->
                        <referencedBy typeCode="REFR">
                            <keyword>
                                <code code="C001" codeSystem="2.16.840.1.113883.3"/>
                            </keyword>
                        </referencedBy>
                        <!--GT001 is the code for the Group Title Keyword Definition "Analytic
Procedures"-->
                        <referencedBy typeCode="REFR">
                            <keyword>
                                <code code="GT001" codeSystem="2.16.840.1.113883.3"/>
                            </keyword>
                        </referencedBy>
                    </contextOfUse>
                </component>
                <component>
```

```
            <priorityNumber value="2000"/>
                <contextOfUse>
                    <id root="4a5c97e1-4448-47e2-90ff-2d6a264167c0"/>
                    <code code="ich-3-2-p-7" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
                    <statusCode code="active"/>
                    <!--Document Referenced is Analytical Procedure 2-->
                    <derivedFrom>
                        <documentReference>
                            <id root="0127b8b6-5510-45c5-93fd-9a3a6e9735aa"/>
                        </documentReference>
                    </derivedFrom>
                    <!--C001 is the code for the Group Title Keyword Definition "PVDC Bilster
Pack"-->
                    <referencedBy typeCode="REFR">
                        <keyword>
                            <code code="C001" codeSystem="2.16.840.1.113883.3"/>
                        </keyword>
                    </referencedBy>
                    <!--GT001 is the code for the Group Title Keyword Definition "Analytic
Procedures"-->
                    <referencedBy typeCode="REFR">
                        <keyword>
                            <code code="GT001" codeSystem="2.16.840.1.113883.3"/>
                        </keyword>
                    </referencedBy>
                </contextOfUse>
            </component>
```

The group of document may change from one Context of Use to many Context of Use elements; and many to one.

8.2.14.2 *One File to Many*

This scenario describes a change in content composition where one file (i.e., document) is being replaced with content being provided by many documents.

Sequence 1- Document Referenced

In the first submission unit, the following Context of Use is provided to show a document reference by a Context of Use.

```
<component>
            <priorityNumber value="1000"/>
                <contextOfUse>
                    <id root="1f271446-8d56-4ddc-b730-eaee208c7053"/>
                    <code code="ich-3-2-p-7" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
                    <statusCode code="active"/>
                    <!--Document Referenced is Analytical Procedure 1-->
                    <derivedFrom>
```

```
                        <documentReference>
                            <id root="164af1e4-f625-4621-8d69-ca56b8f7dc7b"/>
                        </documentReference>
                    </derivedFrom>
                    <!--C001 is the code for the Group Title Keyword Definition "PVDC Bilster
Pack"-->
                    <referencedBy typeCode="REFR">
                        <keyword>
                            <code code="C001" codeSystem="2.16.840.1.113883.3"/>
                        </keyword>
                    </referencedBy>
                    <!--GT001 is the code for the Group Title Keyword Definition "Analytic
Procedures"-->
                    <referencedBy typeCode="REFR">
                        <keyword>
                            <code code="GT001" codeSystem="2.16.840.1.113883.3"/>
                        </keyword>
                    </referencedBy>
                </contextOfUse>
            </component>
```

Sequence 2

The following sample depicts the replacement of the previous Context of Use with two new CoU elements each referencing a document. The Related Context of Use is a reference back to the identifier of the previous Context of Use.

```
            <component>
            <priorityNumber value="2000"/>
                <contextOfUse>
                    <id root="0c0abab8-cbfa-4d2f-9793-2b30ea51b8f5"/>
                    <code code="ich-3-2-p-7" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
                    <statusCode code="active"/>
                    <replacementOf typeCode="RPLC">
                        <relatedContextOfUse>
                            <id root="1f271446-8d56-4ddc-b730-eaee208c7053"/>
                        </relatedContextOfUse>
                    </replacementOf>
                    <!--Document Referenced is Analytical Procedure 1-->
                    <derivedFrom>
                        <documentReference>
                            <id root="164af1e4-f625-4621-8d69-ca56b8f7dc7b"/>
                        </documentReference>
                    </derivedFrom>
                    <!--C001 is the code for the Group Title Keyword Definition "PVDC Bilster
Pack"-->
                    <referencedBy typeCode="REFR">
                        <keyword>
                            <code code="C001" codeSystem="2.16.840.1.113883.3"/>
                        </keyword>
```

```
                    </referencedBy>
                    <!--GT001 is the code for the Group Title Keyword Definition "Analytic
Procedures"-->
                    <referencedBy typeCode="REFR">
                        <keyword>
                            <code code="GT001" codeSystem="2.16.840.1.113883.3"/>
                        </keyword>
                    </referencedBy>
                </contextOfUse>
            </component>
            <component>
            <priorityNumber value="3000"/>
                <contextOfUse>
                    <id root="4a5c97e1-4448-47e2-90ff-2d6a264167c0"/>
                    <code code="ich-3-2-p-7" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
                    <statusCode code="active"/>
                    <replacementOf typeCode="RPLC">
                        <relatedContextOfUse>
                            <id root="1f271446-8d56-4ddc-b730-eaee208c7053"/>
                        </relatedContextOfUse>
                    </replacementOf>
                    <!--Document Referenced is Analytical Procedure 2-->
                    <derivedFrom>
                        <documentReference>
                            <id root="0127b8b6-5510-45c5-93fd-9a3a6e9735aa"/>
                        </documentReference>
                    </derivedFrom>
                    <!--C001 is the code for the Group Title Keyword Definition "PVDC Bilster
Pack"-->
                    <referencedBy typeCode="REFR">
                        <keyword>
                            <code code="C001" codeSystem="2.16.840.1.113883.3"/>
                        </keyword>
                    </referencedBy>
                    <!--GT001 is the code for the Group Title Keyword Definition "Analytic
Procedures"-->
                    <referencedBy typeCode="REFR">
                        <keyword>
                            <code code="GT001" codeSystem="2.16.840.1.113883.3"/>
                        </keyword>
                    </referencedBy>
                </contextOfUse>
            </component>
```

8.2.14.3 *Many Files to One*

This scenario describes the situations where content provided across multiple files is being replaced by content provided as a single file. If the initial sequence sent many Context of Use elements (and

thus multiple documents), a subsequent sequence that wants to reference one file would do so by merging the content into one physical file.

Sequence 1 – Many Documents Referenced

The following sample depicts two ***contextOfUse*** elements, each referencing a document.

```
<component>
    <priorityNumber value="1000"/>
        <contextOfUse>
            <id root="0c0abab8-cbfa-4d2f-9793-2b30ea51b8f5"/>
            <code code="ich-3-2-p-7" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
            <statusCode code="active"/>
            <!--Document Referenced is Analytical Procedure 1-->
            <derivedFrom>
                <documentReference>
                    <id root="164af1e4-f625-4621-8d69-ca56b8f7dc7b"/>
                </documentReference>
            </derivedFrom>
            <!--C001 is the code for the Group Title Keyword Definition "PVDC Bilster
Pack"-->
            <referencedBy typeCode="REFR">
                <keyword>
                    <code code="C001" codeSystem="2.16.840.1.113883.3"/>
                </keyword>
            </referencedBy>
            <!--GT001 is the code for the Group Title Keyword Definition "Analytic
Procedures"-->
            <referencedBy typeCode="REFR">
                <keyword>
                    <code code="GT001" codeSystem="2.16.840.1.113883.3"/>
                </keyword>
            </referencedBy>
        </contextOfUse>
    </component>
    <component>
    <priorityNumber value="2000"/>
        <contextOfUse>
            <id root="4a5c97e1-4448-47e2-90ff-2d6a264167c0"/>
            <code code="ich-3-2-p-7" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
            <statusCode code="active"/>
            <!--Document Referenced is Analytical Procedure 2-->
            <derivedFrom>
                <documentReference>
                    <id root="0127b8b6-5510-45c5-93fd-9a3a6e9735aa"/>
                </documentReference>
            </derivedFrom>
            <!--C001 is the code for the Group Title Keyword Definition "PVDC Bilster
Pack"-->
```

```
                        <referencedBy typeCode="REFR">
                            <keyword>
                                <code code="C001" codeSystem="2.16.840.1.113883.3"/>
                            </keyword>
                        </referencedBy>
                        <!--GT001 is the code for the Group Title Keyword Definition "Analytic
Procedures"-->
                        <referencedBy typeCode="REFR">
                            <keyword>
                                <code code="GT001" codeSystem="2.16.840.1.113883.3"/>
                            </keyword>
                        </referencedBy>
                    </contextOfUse>
                </component>
```

Sequence 2 – One Document Referenced

The following sample shows that the three previous Context of Use elements are replaced by one Context of Use referencing a document (the document now contains all of the content previously submitted in three separate documents).

```
                <component>
                <priorityNumber value="1100"/>
                    <contextOfUse>
                        <id root="49e18e35-fe1b-4929-bf30-ea58c81ec30f"/>
                        <code code="ich-3-2-p-7" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
                        <statusCode code="active"/>
                        <replacementOf typeCode="RPLC">
                            <relatedContextOfUse>
                                <id root="0c0abab8-cbfa-4d2f-9793-2b30ea51b8f5"/>
                            </relatedContextOfUse>
                        </replacementOf>
                        <replacementOf typeCode="RPLC">
                            <relatedContextOfUse>
                                <id root="4a5c97e1-4448-47e2-90ff-2d6a264167c0"/>
                            </relatedContextOfUse>
                        </replacementOf>
                        <!--Document Referenced is Analytical Procedure Consolidated-->
                        <derivedFrom>
                            <documentReference>
                                <id root="e8e44446-de99-4324-ba9c-502fe8d729ba"/>
                            </documentReference>
                        </derivedFrom>
                        <!--C001 is the code for the Group Title Keyword Definition "PVDC Bilster
Pack"-->
                        <referencedBy typeCode="REFR">
                            <keyword>
```

```
                        <code code="C001" codeSystem="2.16.840.1.113883.3"/>
                    </keyword>
                </referencedBy>
                <!--GT001 is the code for the Group Title Keyword Definition "Analytic
Procedures"-->
                <referencedBy typeCode="REFR">
                    <keyword>
                        <code code="GT001" codeSystem="2.16.840.1.113883.3"/>
                    </keyword>
                </referencedBy>
            </contextOfUse>
        </component>
```

8.2.14.4 *Other Considerations*

8.2.14.4.1 *Document Reuse*

A Document can be referenced many times in the life cycle of the application. Therefore, the reuse of documents is an important feature of eCTD v4.0. Reuse of documents can be used when the document accurately represents the content and metadata that should be present under another Context of Use. The most common examples of document reuse will be depicted in this section.

Refer to Regional/Module 1 Implementation Guides for additional information on document retention practices and rules for Document Reuse.

When the same document is being sent within or across submission units, the ***document*** element only needs to be provided once to establish the document identifier, which can then be referenced by any reference in a Context of Use element.

Below, the XML shows two Context of Use elements that reference the same document by its document identifier.

Sequence 1

Context of Use Element

```
<component>
<priorityNumber value="1000"/>
    <contextOfUse>
        <id root="7480bc1a-6486-4714-8d32-a3bd41de9be6"/>
            <code code="ich-3-2-a-3" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1" />
        <statusCode code="active"/>
        <derivedFrom>
            <documentReference>
                <id root="3d1084fb-56c6-4923-a1e5-8a15e4fdc9c5"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

Document.id provided in Sequence 1

Document element

```
<document>
    <id root="3d1084fb-56c6-4923-a1e5-8a15e4fdc9c5"/>
    <title value="Excipients X"/>
    <text integrityCheckAlgorithm="SHA256">
        <reference value=".../m3/32-prod/excipients.pdf"/>
        <integrityCheck>c0d5623550c997a70b62717d95fca1cada201754d1ed9fbbbbfa97bfd64c8ea4
    </integrityCheck>
    </text>
</document>
```

Document.id

Sequence 2

Context of Use Element

```
<component>
<priorityNumber value="2000"/>
    <contextOfUse>
        <id root="12345678-1234-1234-1234-123456090239"/>
        <code code="ich-3-2-a-3" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1" />
        <statusCode code="active"/>
        <derivedFrom>
            <documentReference>
                <id root="3d1084fb-56c6-4923-a1e5-8a15e4fdc9c5"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

Document.id provided in Sequence 1

Document Element

The ***document*** element is not sent in this submission unit. The document was sent in the previous sequence 1.

8.2.14.4.2 *Document Title Updates*

If the sender has sent a ***document*** element with an error in the ***document.title*** element, it can be updated without creating an entirely new document. The example provided in this section, will indicate the required elements for such an update.

2.16.840.1.113883.3.989.2.2.4.1.1

Initial submission of document

```
<document>
    <id root="ceb05f3d-ebb0-4547-9734-056efa134a7a"/>
    <title value="Process and Controls"/>
    <text integrityCheckAlgorithm="SHA256">
```

```
        <reference value=".../m3/32-prod/manuf-process-and-controls.pdf"/>
        <integrityCheck>a4c828974a7d177137d69aedfc45379a694611ef317c6c1741a935aa9555c57
    d</integrityCheck>
    </text>
</document>
```

Update to Document Title using updateMode

```
<document>
    <id root="ceb05f3d-ebb0-4547-9734-056efa134a7a"/>
    <title value="Manufacturing Process and Controls" updateMode="R"/>
</document>
```

8.2.14.4.3 *File Reuse*

A file is usually represented by one ***document*** element and that ***document*** element can be referenced by multiple ***ContextofUse*** elements. This is described in the Document Reuse section. In certain situations, a file may need to be presented differently in one usage versus another (e.g., different document title). In these rare situations the file would need to be represented by an additional ***document*** element. Thus the same file path may appear in multiple ***document.text*** elements. The file only needs to be sent once in the folder structure. This is described in the Document Reuse section (See section 8.2.14.3.1).

Files can be reused across submissions and applications (see note below) by providing the file path of a previously submitted file when defining a new ***document*** element for that submission or application. The file will be retrieved from its original folder location.

Note: if files are reused, i.e., sent once in the original folder structure, the manual navigation of the folder structure will become more difficult as all files within a submission unit, submission or application may not be contained in the same physical folder location.

Note: Refer to Regional/Module 1 Implementation Guides for region-specific information about file reuse.

The following XML sample describes a ***document*** element with the title "Report for Study 1" and a document code identifying it as a study report body.

```
<component>
    <document>
        <id root="bab246ef-7d8e-4042-bd8b-ad9769f4589b"/>
        <title value="Report for Study 1"/>
        <text integrityCheckAlgorithm="SHA256" language="en">
            <reference value="../m5/531-biopharm/report1.pdf"/>
            <integrityCheck>5b94eb14cd31031a4d4539d0bcfbef028a91c04d2d2575990c4422947a9f
            437a</integrityCheck>
        </text>
    </document>
</component>
```

The following ***document*** element describes the same file from the previous example with a slightly different document title. This ***document*** element is being created in a subsequent submission unit from the original submission of the file; notice the difference in the file path information provided in these examples.

```
<component>
    <document>
        <id root="79da2f37-02a8-4dcd-8552-54565b093c08"/>
        <title value="Summary Report for Study 1"/>
        <text integrityCheckAlgorithm="SHA256" language="en">
            <reference value="../../second-level-folder/m5/531-biopharm/report1.pdf"/>
            <integrityCheck>
44f4ccef9117c39df755701a4ee564864562167b3eb6ea770e30edabddc535fd</integrityCheck>
        </text>
    </document>
</component>
```

8.2.15 Keyword Definition

The ***keywordDefinition*** is used to define a sender-specified keyword that will be referenced by a code in other parts of the message. The use of keyword definitions is mainly for defining keyword values that are not defined by a controlled vocabulary (e.g., sender-specific keywords). A keyword definition contains name value pairs that are used to provide Keywords on the Context of Use.

8.2.15.1 *Location in XML*

The ***keywordDefinition*** element in the XML message is in the following location for keyword definitions:

- ***controlActProcess***>> ***subject***>> ***submissionUnit***>>***componentOf***>>***submission***>> ***componentOf***>>***application***>> ***referencedBy***> ***keywordDefinition***

There may be ***informationRecipient***, ***holder, reference*** or ***subject*** elements prior to the ***referencedBy*** element.

Refer to Table 5: XML Structure for the XML representation.

8.2.15.2 *XML Elements*

The following tables provide a complete set of XML elements and attributes required for the ***keywordDefinition*** element, and any special instructions.

The ***classCode*** and ***moodCode*** are not required in the eCTD v4.0 XML message. The ***classCode*** is fixed to "ACT" and ***moodCode*** is fixed to "EVN". If the XML message contains any other values for these attributes it will be invalid against the schema.

Each ***keywordDefinition*** should be sent in its own ***keywordDefinition*** element. Although the schema allows multiple values for each ***keywordDefinition***, the eCTD v4.0 only allows one item per ***keywordDefinition*** element.

Conditions that apply to the ***keywordDefinition*** element:

- Zero to many ***keywordDefinition*** elements can be sent for each ***application*** element
- A ***keywordDefinition*** should be provided for sender-specified keywords.
- The ***keywordDefinition*** only needs to be provided once for an Application – i.e., the keyword definition should be defined once and referenced by its assigned code value. Note: the ***keywordDefinition*** will need to be defined for each new Application.

8.2.15.2.1 *keywordDefinition.code*

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
code		[1..1]		This is the container element that identifies the type of keyword definition.
	Code	[1..1]	Alpha Numeric *e.g., "ich-manufacturer"*	This is the ***code*** attribute for the coded value of the type of keyword definition.
	codeSystem	[1..1]	Valid OID	This is the ***codeSystem*** OID that is a unique identifier for the controlled vocabulary system. *This should be the OID registered for the code system.*
Conformance	The ***code*** and ***codeSystem*** are required attributes.			
Business Rules	The ***code*** must be from a valid ICH Keyword code type.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***code.displayName*** • ***code.originalText*** • ***code.translation*** • ***code.source*** • ***code@codeSystemName*** • ***code@codeSystemVersion*** • ***code@valueSet*** • ***code@valueSetVersion*** • ***code@codingRationale*** • ***code@validTimeLow*** • ***code@validTimeHigh*** • ***code@controlInformationRoot*** • ***code@controlInformationExtension*** • ***code@nullFlavor*** • ***code@flavorId*** • ***code@updateMode***			

1852 8.2.15.2.2 ***keywordDefinition.statusCode***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
statusCode		[1..1]		This is the container element that identifies the status of the ***keywordDefinition***.
	Code	[1..1]	Alpha *e.g., active*	This is the code value for the status.
Conformance	The ***statusCode*** is required.			
Business Rules	The ***code*** attribute should always have a value of “active”.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***statusCode.part*** • ***statusCode@validTimeLow*** • ***statusCode@validTimeHigh*** • ***statusCode@controlInformationRoot*** • ***statusCode@controlInformationExtension*** • ***statusCode@nullFlavor*** • ***statusCode@flavorId*** • ***statusCode@updateMode***			

1853 8.2.15.2.3 ***keywordDefinition.value***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
value		[1..1]		This is the container element for the keyword defined for the keyword code provided for ***keywordDefinition***.
value.item		[1..1]		This is the container element to specify an individual keyword identifier.
	Code	[1..1]	Alpha Numeric Sender specified value *e.g., MANU001*	This is the ***code*** attribute for the keyword being defined.
	codeSystem	[1..1]	Valid OID	This is the ***codeSystem*** OID that is a unique identifier for the controlled vocabulary system.

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
value.item.displayName		[1..1]		This is the container element to specify the ***displayName,*** which is the value of the keywordDefinition code.
	Value	[1..1]	Alpha Numeric *Sender specified value e.g., "Big Manufacturer"*	The ***displayName*** attribute of the ***value*** element of the keyword being defined.
	updateMode	[0..1]	Alpha *e.g., R=Replace*	The ***updateMode*** should be used to make changes to the Keyword Definition's display name value.
Conformance	***The keywordDefinition.value*** is a required element. The ***value.item@code, value.item@codeSystem*** and ***value.item.displayName@value*** are required attributes.			
Business Rules	Each ***keywordDefinition*** can only contain one sender-specified keyword. The ***displayName@value*** is the only attribute that can be updated, at which time the ***displayName@updateMode*** should only be provided with a value of "R". The ***updateMode*** should not be used unless the ***displayName@value*** is being changed – i.e., avoid using update mode if the value is not being updated for the keyword definition.			
Excluded Elements and/or Attributes	The following elements and attributes may not be required by eCTD v4.0: • ***displayName@controlInformationExtension*** • ***displayName@controlInformationRoot*** • ***displayName@flavorId*** • ***displayName@language*** • ***displayName@nullFlavor*** • ***displayName@validTimeHigh*** • ***displayName@validTimeLow***			

1854

8.2.15.3 *Terminology*

All terminology will be provided as genericode files or in a spreadsheet for Step 2.[24]

8.2.15.4 *Excluded Elements*

No elements are excluded for the ***keywordDefinition*** element.

8.2.16 XML SAMPLES: Keyword Definition

At this time, keywords should only be defined for an application – i.e., keyword definitions should not be reused across applications. The following sections outline the additional scenarios for XML instances in defining and using keywords.

8.2.16.1.1 *Keyword Definitions*

The following XML sample shows one ***keywordDefinition*** of type, manufacturer.

```
<referencedBy>
    <keywordDefinition>
        <code code="ich-manufacturer-3"
        codeSystem="2.16.840.1.113883.3.989.2.2.4.1.2"/>
        <statusCode code="active"/>
        <value>
            <item code="MANU001" codeSystem="CompanyOID-
        ManufacturerKeyword">
                <displayName value="Big Manufacturer"/>
            </item>
        </value>
    </keywordDefinition>
</referencedBy>
```

Note: that one item value per keyword definition is required; the schema allows for multiple.

See XML Color Legend for color usage.

8.2.16.1.2 *Keyword Definition display name change*

Keyword Definitions that are sent may have been sent with errors. If the sender needs to correct the display name of a keyword definition (i.e., it is the same concept or term with a correct representation (e.g., spelling)) only the display name may be altered. The keyword definition code shall remain the same.

Sequence 1

```
<referencedBy>
    <keywordDefinition>
```

[24] Final Implementation Terminology will be provided on the ESTRI website.

```
            <code code="ich-manufacturer-3"codeSystem="2.16.840.1.113883.3.989.2.2.4.1.2"/>
            <statusCode code="active"/>
            <value>
                <item code="MANU001" codeSystem="CompanyOID-ManufacturerKeyword">
                    <displayName value="Ace Manufacturer"/>
                </item>
            </value>
        </keywordDefinition>
    </referencedBy>
```

Sequence 2

```
    <referencedBy>
        <keywordDefinition>
            <code code="ich-manufacturer-3"codeSystem="2.16.840.1.113883.3.989.2.2.4.1.2"/>
            <statusCode code="active"/>
            <value>
                <item code="MANU001" codeSystem="CompanyOID-ManufacturerKeyword">
                    <displayName value="Acme Manufacturer" updateMode="R"/>
                </item>
            </value>
        </keywordDefinition>
    </referencedBy>
```

displayName changed to correct value.

Note: Refer to Regional/Module 1 Implementation Guides for information on the keyword definition display name when it needs to be updated in just the referenced submission or for all uses in the application.

8.2.16.1.3 *Use of Keyword Definitions across Submission Units*

Keyword Definitions once they have been sent by the sender do not need to be sent again unless there is a change to the definition. The keyword code shall stay the same across submission units within an application – i.e., only the display name can be changed. There should only be one keyword definition code and display name pair defined for a particular concept – i.e., one concept shall not be defined more than once within an application.

Sequence 1

Keyword Defined in Sequence 1

```
        <referencedBy>
            <keywordDefinition>
                <code code="ich-manufacturer-3"codeSystem="2.16.840.1.113883.3.989.2.2.4.1.2"/>
                <statusCode code="active"/>
                <value>
                    <item code="MANU003" codeSystem="CompanyOID-ManufacturerKeyword">
                        <displayName value="Simple Manufacturer"/>
                    </item>
                </value>
            </keywordDefinition>
        </referencedBy>
```

Keyword Definition used by Context of Use in Sequence 1

```
<component>
<priorityNumber value="1000"/>
    <contextOfUse>
        <id root="8c590801-c4ca-4940-bb4d-5a4cd32685d7"/>
        <code code="ich-3-2-s-2-3" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
        <statusCode code="active"/>
        <derivedFrom>
        <!--Document titled "Controls for Material YYY"-->
            <documentReference>
                <id root="d0c6463c-7538-4ac8-827d-65b083c3893d"/>
            </documentReference>
        </derivedFrom>
        <referencedBy typeCode="REFR">
            <keyword>
                <code code="MANU003" codeSystem="2.16.840.1.113883.X"/>
            </keyword>
        </referencedBy>
        <referencedBy typeCode="REFR">
            <keyword>
                <code code="SUB001" codeSystem="2.16.840.1.113883.X"/>
            </keyword>
        </referencedBy>
    </contextOfUse>
</component>
```

Sequence 3

Keyword Defined in Sequence 3

No additional information sent in the XML for the Keyword Definition. The value sent in sequence 1, “MANU003” with display name “Simple Manufacturer” is still applicable.

Keyword Definition used by Context of Use in Sequence 3

```
<component>
    <priorityNumber value="2000"/>
    <contextOfUse>
        <id root="64e51fb8-4608-4c3a-af52-68b5cc02345b"/>
        <code code="ich-3-2-s-2-3" codeSystem="2.16.840.1.113883.3.989.2.2.4.1.1"/>
        <statusCode code="active"/>
        <derivedFrom>
        <!--Document titled “Controls for Material BCD”-->
            <documentReference>
                <id root="23967c61-99bf-4090-863c-15b524ee242e"/>
            </documentReference>
        </derivedFrom>
        <referencedBy typeCode="REFR">
            <keyword>
                <code code="MANU003" codeSystem="2.16.840.1.113883.X"/>
            </keyword>
        </referencedBy>
        <referencedBy typeCode="REFR">
            <keyword>
                <code code="SUB001" codeSystem="2.16.840.1.113883.X"/>
            </keyword>
        </referencedBy>
    </contextOfUse>
</component>
```

9. DOSSIER MANAGEMENT

Dossier Management refers to the life cycle management of submission units, submissions (e.g., regulatory activities) and applications. Although this topic is very important to eCTD v4.0, it is not covered in this Implementation Guide. Due to the variation in regulatory processes across regions as to how to manage the life cycle as well as the precise definition of these concepts in each region, this information will be found in the Regional/Module 1 Implementation Guides.

10. COMPATIBILITY AND REFERENCE TO ECTD V3.2.2

[This section should describe how to continue an eCTD life cycle started with v3.x using the v4.0 specification. This should include topics like how to reference eCTD v3.x leafs and sequences from within eCTD v4.0 messages, mapping of controlled vocabulary terms used in v3.x into v4.0, how to handle file-tags, and any expectations on the display of information from v3.x sequences from tools for displaying v4.0 messages.

This section will include commented examples to show the transition/migration of eCTD v3.2.2 messages into the eCTD v4.0 format.

We should also define what an applicant should do with sequence numbers if there is an existing eCTD. Should they start from sequence 1 with eCTD v4.0 (will this cause confusion in having a sequence 0001 and 1) or continue from existing numbering e.g. sequence 11 in eCTD v4.0 would follow 0010 in eCTD v3.x.]

[NOTE: No content for Forward Compatibility in this version of the document. Subsections will be added as ICH defines the various compatibility areas. Refer to Regional/Module 1 Implementation Guides for additional information for each region.]

Need to address:

- eCTD v3.2.2 - ICH and Regional IGs (v3.2 DTD)
- STF v2.6.1 – Regional IG (v2.2 DTD) Need to harmonize with HC on this topic for regional consideration

11. APPENDIX 1: SAMPLE FILES AND FOLDERS FOR MODULES 2-5

With increased document reuse in eCTD v4.0, the folder structure will no longer serve as a reliable mechanism to navigate through the submission content. The folder structure for Modules 2-5 is presented below. Additional folders should only be included for technical reasons (e.g., providing files with the same name) and should only be placed at the lowest level of the folder structure as specified in each of the subsections below.

11.1 Module 2 Summaries

The files in this module should be provided as PDF text with the exception of a few embedded images, when needed. The name of the folder for module 2 should be m2. No additional folders are necessary in this module. The m2 folder structure is depicted in Figure 5: Module 2 Folder Structure as a single folder.

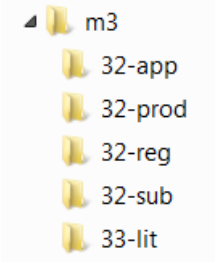
Figure 5: Module 2 Folder Structure

11.2 Module 3 Quality

The name of the folder for module 3 should be m3. The folders in module 3 should be named as follows but can be further reduced or omitted to minimize path length issues. Additional folders should only be provided to organize files with the same name.

The m3 folder structure is depicted in Figure 6: Module 3 Folder Structure.

Figure 6: Module 3 Folder Structure

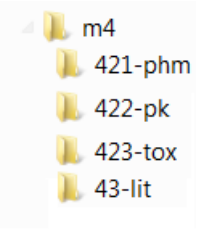


Section in CTD	Description	Folder Name
3.2.A	Appendices	*32-app*
3.2.P	Drug Product (name, dosage form)	*32-prod*
3.2.R	Regional Information	*32-reg*
3.2.S	Drug Substance	*32-sub*
3.3	Literature References	*33-lit*

11.3 Module 4 Nonclinical Study Reports

The name of the folder for module 4 should be m4. The folders in module 4 should be named as follows but can be further reduced or omitted to minimize path length issues. The m4 folder structure is depicted in Figure 7: Module 4 Folder Structure.

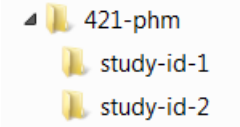
Figure 7: Module 4 Folder Structure



Section in CTD	Description	Folder Name
4.2.1	Pharmacology	*421-phm*
4.2.2	Pharmacokinetics	*422-pk*
4.2.3	Toxicology	*423-tox*
4.3	Literature References	*43-lit*

Additional folders may be added to organize study files, which may be required to allow multiple files with the same name. The folders should be named with the study identifier number (e.g., study-id-1). Refer to Regional/Module 1 Implementation Guides for rules additional folders in this module.

Figure 8: Example of Study folders



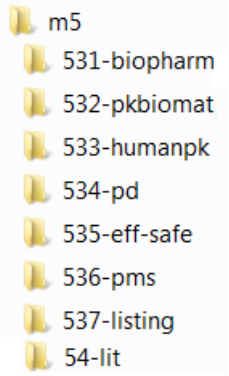
11.4 Module 5 Clinical Study Reports

The name of the folder for module 5 should be m5. The folders in module 5 should be named as follows but can be further reduced or omitted to minimize path length issues.

- The CTD organization provides locations for case report forms and individual patient data listings in Module 5.3.7. See Regional/Module 1 Implementation Guides for additional guidance for case report forms, data sets and individual patient data listings
- In the eCTD v4.0, files for publications and literature references should be located in the folder for Module 5.4.

The m5 folder structure is depicted in Figure 9: Module 5 Folder Structure

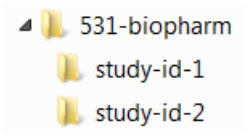
Figure 9: Module 5 Folder Structure



Section in CTD	Description	Folder Name
5.3.1	Reports of Biopharmaceutic Studies	*531-biopharm*
5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials	*532-pkbiomat*
5.3.3	Reports of Human Pharmacokinetic (PK) Studies	*533-humanpk*
5.3.4	Reports of Human Pharmacodynamic (PD) Studies	*534-pd*
5.3.5	Reports of Efficacy and Safety Studies	*535-eff-safe*
5.3.6	Reports of Postmarketing Experience	*536-pms*
5.3.7	Case Report Forms and Individual Patient Listings[6]	*537-listing*
5.4	Literature References	*54-lit*

Additional folders may be added to organize study files, which may be required to allow multiple files with the same name. The folders should be named with the study identifier number (e.g., study-id-1). Refer to Regional/Module 1 Implementation Guides for rules additional folders in this module.

Figure 10: Example of Study Folders



12. APPENDIX 2: VALIDATION OF THE ECTD V4.0 MESSAGE

Condense this section to minimal information and reference to Regional/Module 1 IGs.

The validation of the eCTD v4.0 message will not only include the general schema validation, against the ICH eCTD v4.0 Schema, but also additional business rules that are documented in this Implementation Guide and the Regional/Module 1 Implementation Guide.

For specific conformance and business rules for the eCTD v4.0 message, refer to each element specification in Section 8.2.

- Conformance – these statements should be enforced by the schema, e.g., cardinality, but in some cases the cardinalities have conditions and in certain situations, the element or attribute are required. Those items will be specified in each of the Required XML Element tables.

- Business Rules – these are additional rules that are not enforced by the schema, but based on consensus within ICH, these rules have been set for the eCTD v4.0 message. These business rules will invoke additional requirements for regulatory authorities and regulated industry.

The remaining validation rules are found in this section of the document, both in summary and detailed versions.

12.1 Summary of Validation Rules

The following section outlines the validation rules by type or element. Additional details are in the subsections below.

Category	Type/Element	Validation Criteria
Message Validation	**Schema**	Message must be Well Formed XML based on XML 1.0.
		Message must be valid against the ICH specified version of the RPS schema
	Submission Unit	Submission Unit identifier is required (1..1)
		Submission Unit id root must be a unique identifier
		Only one Submission Unit element can exist for a message.
		Submission Unit code value is required (1..1)
		Submission Unit must have a valid code value
		Submission Unit Code System value is required (1..1)
		Submission Unit code must have a valid OID for the Code System value
		The Submission Unit status code requires the code attribute "active"
	Sequence Number	Sequence Number is required (1..1)
		Sequence Number must be a whole number
		Sequence Number for initial submission unit starts with 1
		Sequence Number is unique in the application for the applicant
		The Sequence Number must have one and only one value for the Submission element

Category	Type/Element	Validation Criteria
	Priority Number (CoU)	CoU Priority Number is required
		CoU Priority Number must be a non-negative real number
		CoU Priority Number shall have one and only one value
	Context of Use	CoU identifier is required
		CoU id root must be a unique identifier
		CoU status code element is required
		CoU status code value can only be “active” or “suspended”
	Related Context of Use	RelatedCoU identifier is required when RelatedCoU is provided
	Document Reference	DocumentReference identifier is required for all active CoU elements
		DocumentReference element not allowed for suspended CoU elements
	Keyword	Keyword code is required for each keyword element on a CoU
		Keyword code system is required for each keyword element
		Keyword code system must be a valid OID
		Keyword code system must have a valid value
	Submission	Submission identifier is required (1..1)
		Submission code is required (1..1)
		Submission code must have a valid value for the region
		Submission code system is required (1..1)
		Submission code system must have a valid regional code system OID
	Application	Application identifier is required (1..1)
		Application code is required
		Application code must have a valid value
		Application code system is required
		Application code system is a valid OID
	Document	Document identifier is required (1..1)
		Document id root must be a unique identifier
		Document identifier must have a valid value
		Document identifier is unique (i.e., it is not a duplicate identifier and not an update to a document title)
		Document title is required
		Document text element requires a checksum value unless a document title update is submitted (i.e., this is the only scenario making this element optional)
		Document text element requires a valid checksum value unless a document title update is submitted (i.e., this is the only scenario making this element optional)

Category	Type/Element	Validation Criteria
		Document path is required unless the document title update is submitted (i.e., this is the only scenario making this element optional)
		Document path does not exist unless the document title update is submitted (i.e., this is the only scenario making this element optional)
	Keyword Definition	Keyword definition code is required (1..1)
		Keyword definition code must have a valid value
		Keyword definition value code is required (1..1)
		Keyword definition value code must have a valid value
		Keyword definition value is required (1..1)
		Keyword definition value has one and only one value.item element
		Keyword definition display name value is required
Submission Package	**Submission Package**	Submission File Name
		Submission File quantity
		Submission File location
		File name format
		Document checksum is validated against the document's calculated checksum
		File name length
		Folder name length
		Folder path length

12.1.1 Message Validation Rules

These are validation criteria that can either be passed or failed. eCTDs that fail to meet one or more of these criteria will be returned to the applicant for fixing and resubmission as the same sequence number.

No Unique ID	**Category**	Validation Criteria	Issue Description	Corrective Action
Schema				
eCTD 4-001	Schema	Message must be Well Formed XML based on XML 1.0.	The XML is not well-formed according to the version of the XML standard.	The XML must be corrected to become well-formed.
eCTD 4-002	Schema	Message must be valid against the ICH specified version of the RPS schema	The message is not valid against the current ICH specified version of the RPS schema	The XML should be corrected to meet all of the schema validations.
Submission Unit				
eCTD 4-003	Schema	Submission Unit identifier is required (1..1)	***SubmissionUnit.id@root*** is not provided	The submission unit needs to be resubmitted with a value for ***id@root*** for the submission unit.
eCTD 4-004	Business Rule	Submission Unit id root must be a unique identifier	***SubmissionUnit.id@root*** is not unique	The submission unit needs to be resubmitted with the unique identifier for the submission unit element.
eCTD 4-005	Business Rule	Only one Submission Unit element can exist for a message.	The message has more than one submission unit in a message payload	The submission unit needs to be resubmitted with only one submission unit included.
eCTD 4-006	Schema	Submission Unit code value is required (1..1)	The ***SubmissionUnit.code@code*** value is not provided	The submission unit needs to be resubmitted with a code value.
eCTD 4-007	Business Rule	Submission Unit must have a valid code value	The ***SubmissionUnit.code@code*** is not a valid value (for the region)	The submission unit needs to be resubmitted with a valid code value.
eCTD 4-008	Business Rule	Submission Unit Code System value is required (1..1)	The ***submissionUnit.code@codeSystem*** is not provided	The submission unit needs to be resubmitted with a valid code value.

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-009	Schema	Submission Unit code must have a valid OID for the Code System value	The ***submissionUnit.code@codeSystem*** is not a valid registered or known OID	The submission unit needs to be resubmitted with a valid code system OID.
eCTD 4-010	Business Rule	The Submission Unit status code requires the code attribute “active”	The submission unit does not have a status code value of active	The submission unit needs to be resubmitted with an active status code.
Sequence Number				
eCTD 4-011	Business Rule	Sequence Number is required (1..1)	The sequence number value is not provided	The submission unit may need to be resubmitted with a sequence number.
eCTD 4-012	Business Rules	Sequence Number must be a whole number	The sequence number value is not a whole number	The submission unit may need to be resubmitted with a correctly formatted sequence number
eCTD 4-013	Business Rule	Sequence Number for initial submission unit starts with 1	The sequence number for the initial submission unit in an application does not start with 1.	The submission unit needs to be resubmitted with the sequence number starting with 1.
eCTD 4-014	Business Rule	Sequence Number is unique in the application for the applicant	The sequence number is not unique in a submission/application	The submission unit needs to be resubmitted to make the sequence number unique for the application.
eCTD 4-015	Business Rule	The Sequence Number must have one and only one value for the Submission element	The Sequence Number does not have one and only one value for each Submission in the submission unit.	The submission unit needs to be resubmitted providing a value. The submission unit needs to be resubmitted to be different than the values that exist for the submission/ application.
Priority Number				
eCTD 4-016	Schema	CoU Priority Number is required	The priority number value is not provided.	The submission unit would need to be resubmitted providing priority numbers.

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-017	Business Rules	CoU Priority Number must be a non-negative real number	The priority number value is not a non-negative real number	The submission unit would need to be resubmitted with non-negative real numbers for the priority number value.
eCTD 4-018	Schema	CoU Priority Number shall have one and only one value	There is more than one CoU priority number provided for each CoU	The submission unit would need to be resubmitted providing priority numbers.
Context of Use				
eCTD 4-018	Schema	CoU identifier is required	The ***ContextOfUse.id@root*** is not provided	The submission unit needs to be resubmitted providing a CoU identifier.
eCTD 4-019	Schema	CoU id root must be a unique identifier	The ***ContextOfUse.id@root*** value is not unique	The submission unit needs to be resubmitted with a unique CoU identifier.
eCTD 4-020	Schema	CoU status code element is required	The CoU statusCode element is not provided.	The submission unit needs to be resubmitted with a status code for each CoU.
eCTD 4-021	Schema	CoU status code value can only be “active” or “suspended”	The ***CoUstatusCode@code*** value is not “active” or “suspended”.	The submission unit needs to be resubmitted with a valid status code for the CoU.
Related Context of Use				
eCTD 4-022	Schema	RelatedCoU identifier is required when RelatedCoU is provided	***RelatedCoU.id@root*** attribute is not provided.	The submission unit needs to be resubmitted providing a relatedCoU identifier.
Document Reference				
eCTD 4-023	Business Rule	DocumentReference identifier is required for all active CoU elements	***DocumentReference.id@root*** attribute is not provided when the Context of Use is active	The submission unit needs to be resubmitted with a Document Reference identifier when the CoU is active.

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-024	Schema	DocumentReference element not allowed for suspended CoU elements	Document Reference element is provided when the Context of Use is suspended	The submission unit needs to be resubmitted without a Document Reference when the CoU is suspended.
Keyword				
eCTD 4-025	Schema	Keyword code is required for each keyword element on a CoU	***Keyword.code@code*** attribute is not provided.	The submission unit needs to be resubmitted providing a Keyword code for each CoU.
eCTD 4-026	Schema	Keyword code system is required for each keyword element	The ***Keyword.code@codeSystem*** is not provided.	The submission unit needs to be resubmitted providing a Keyword code system for each Keyword code.
eCTD 4-027	Schema	Keyword code system must be a valid OID	***Keyword.code@codeSystem*** is not a valid registered or known OID	The submission unit needs to be resubmitted with a valid keyword code system.
eCTD 4-028	Business Rule	Keyword code system must have a valid value	The keyword code is not part of the external controlled vocabulary or defined in the application's keyword definitions	The submission unit needs to be resubmitted with a valid code system for the keyword code.
Submission				
eCTD 4-029	SchemaRules	Submission identifier is required (1..1)	Submission ***id@root*** is not provided.	The submission unit needs to be resubmitted with a submission identifier.
eCTD 4-030	SchemaRules	Submission code is required (1..1)	***Submission.code@code*** attribute is not provided	The submission unit needs to be resubmitted providing a Submission code.
eCTD 4-031	Business rules	Submission code must have a valid value for the region	***Submission.code@code*** is not a valid value.	The submission unit needs to be resubmitted with valid Submission code.

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-032	Schema	Submission code system is required (1..1)	***Submission.code@codeSystem is*** not provided	The submission unit needs to be resubmitted providing a Submission code system.
eCTD 4-033	Business rules	Submission code system must have a valid regional code system OID	***Submission.code@codeSystem*** is not a valid, registered or known OID	The submission unit needs to be resubmitted with a valid Submission code system.
Application				
eCTD 4-034	Schema	Application identifier is required (1..1)	***Application.id.item@root*** is not provided.	The submission unit needs to be resubmitted with an application identifier.
eCTD 4-035	Schema	Application code is required	***Application.code@code*** attribute is not provided.	The submission unit needs to be resubmitted providing an Application code.
eCTD 4-036	Business Rule	Application code must have a valid valude	***Application.code@code*** is not a valid value.	The submission unit needs to be resubmitted with a valid Application code value.
eCTD 4-037	Schema	Application code system is required	***Application.code@codeSystem*** is not provided.	The submission unit needs to be resubmitted providing an Application code system.
eCTD 4-038	Business Rule	Application code system is a valid OID	***Application.code@codeSystem*** is not a valid OID. If the OID does not link to a valid code system and value, the information may not be interpretable.	The submission unit needs to be resubmitted with a valid Application code system.
Document				
eCTD 4-039	Schema	Document identifier is required (1..1)	Document ***id@root*** is not provided	The submission unit needs to be resubmitted providing the Document identifier.

No Unique ID	**Category**	Validation Criteria	Issue Description	Corrective Action
eCTD 4-040	Business Rules	Document identifier must have a valid value	The document identifier is not a valid value.	The submission unit needs to be resubmitted with a corrected valid document identifier.
eCTD 4-062	Business Rules	Document id root must be a unique identifier	The ***Document.id@root*** value is not unique	The submission unit needs to be resubmitted with a unique Document identifier.
eCTD 4-041	Business Rules	Document identifier is unique (i.e., it is not a duplicate identifier)	The document identifier is not unique.	The submission unit needs to be resubmitted with a correction to the unique identifier.
eCTD 4-042	Business Rules	Document title is required	Document ***document.title@value*** does not have a value or does not exist.	The submission unit needs to be resubmitted with a corrected document title value for all documents
eCTD 4-043	Business Rules	Document text element requires a checksum value	*The* ***document.text.integrity Check*** value is not provided for the document element	The submission unit needs to be resubmitted with a checksum value for all documents
eCTD 4-044	Business Rules	Document text element requires a valid checksum value	The document ***document.text.integrity Check*** value is not a valid checksum	The submission unit needs to be resubmitted with a valid checksum value for all documents
eCTD 4-045	Schema	Document path is required	The ***document.text.reference @value*** is not provided	The submission unit needs to be resubmitted with a document path for all documents
eCTD 4-046	Business Rule	Document path does not exist	The document path provided in the eCTD XML does not physically exist	The submission unit needs to be resubmitted with a correct document path.
Keyword Definition				
eCTD 4-047	Business Rule	Keyword definition code is required (1..1)	The ***keywordDefinition.code @code*** is not provided	The submission unit needs to be resubmitted with a keyword definition code

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-048	Business Rule	Keyword definition code must have a valid value	The ***keywordDefinition.code@code*** is not a valid value	The submission unit needs to be resubmitted with a valid keyword definition code
eCTD 4-049	Business Rule	Keyword definition value code is required (1..1)	The ***keywordDefinition.value.item@code*** is not provided	The submission unit needs to be resubmitted with a keyword definition value code
eCTD 4-050	Business Rule	Keyword definition value code must have a valid value	The ***keywordDefinition.value.item@code*** is not a valid value	The submission unit needs to be resubmitted with a valid keyword definition value code
eCTD 4-051	Business Rule	Keyword definition value is required (1..1)	The ***KeywordDefinition.value*** element is not provided	The submission unit needs to be resubmitted with a valid keyword definition value
eCTD 4-052	Business Rule	Keyword definition value has one and only one value.item element	More than one ***KeywordDefinition.value.item*** element is provided	The submission unit needs to be resubmitted with a one ***value.item*** element per keyword definition value
eCTD 4-053	Business Rule	Keyword definition display name value is required	The ***KeywordDefinition.value.item.displayName@value*** is not provided.	The submission unit needs to be resubmitted providing a ***keywordDefinition.value.item.displayName@value***

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No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-054	Business Rule	Submission File Name	The submission file name is not submissionunit.xml	The filename should be corrected to the specified naming convention required for eCTD v4.x.
eCTD 4-055	Business Rule	Submission File quantity	There is more than one submissionunit.xml file included in the submission package.	The submission unit needs to be resubmitted with just one submissionunit.xml file.

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-056	Business Rule	Submission File location	The submissionunit.xml file is not placed at the correct location in the folder structure to be detected by receiving systems	The submission unit needs to be resubmitted with the submissionunit.xml placed in the top-level of the directory of the submission contents package.
eCTD 4-057	Business Rule	File name format	The file does not follow the naming convention instructions – i.e., lower case is not used	The submission unit needs to be resubmitted with the correct file naming convention for all documents.
eCTD 4-058	Business Rule	Document checksum is validated against the document's calculated checksum	The Document checksum(s) of eCTD XML (see validation rules for message – specifically the text element) is not the same as checksum of the file in the folder	The submission unit needs to be resubmitted with the correct checksum for the submitted document.
eCTD 4-059	Business Rule	File name length	The file name length exceeds the allowable number of characters. Note: 64 characters allowed	The submission unit needs to be resubmitted with file names that meet the 64 character limit.
eCTD 4-060	Business Rule	Folder name length	The folder name length exceeds the allowable number of characters. Note: 64 characters allowed	The submission unit needs to be resubmitted with folder names that meet the 64 characters allowed.
eCTD 4-061	Business Rule	Folder path length	The folder path length exceeds the allowable number of characters. Note: 180 characters allowed	The submission unit needs to be resubmitted with the folder path within the 180 characters allowed.

Note: The following Appendices are not complete in this version

13. APPENDIX 3 SAMPLE eCTD MESSAGES

Note: Placeholder for complete eCTD v4.0 Message for each Region.

14. APPENDIX 4 ABBREVIATIONS, TERMS AND DEFINITIONS

[This section will include definitions that relate to the eCTD and HL7/RPS terms]

15. APPENDIX 5 REFERENCES

[This section will include references to procedures described in the IG (e.g., The MD5 Message-Digest Algorithm).]