THE INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH M8 Expert Working Group

ICH Electronic Common Technical Document (eCTD) v4.0 Implementation Guide v1.6

21 May 2024

DOCUMENT CHANGE HISTORY

Version	Date	Comments
1.0	10 December 2015	Initial Step 4 document.
1.1	20 January 2016	Minor editorial corrections after Step 4 approval and sign-off.
1.2	10 November 2016	Revisions based on M8 Review and the following change requests: 00070, 00080, 00090, 00110, 00120, 00150, 00170, 00180, 00220, 00230, 00270, 00300, 00330, 00440, 00450, and 00460. Revised references related to "document groups" to now reference "context groups" (see Common Abbreviations and Terms).
1.3	5 June 2018	Revisions to the eCTD v4.0 Implementation Guide include the following change requests: Cardinality of Data Elements (00520), Validation Rules (00530, 00560), Document element changes, Document Label (00550), Study Group Order (00540), and additional M8 discussion topics (e.g., change in delimiter used for StudyID_Study Title keyword value, and general guidance for sender-defined keywords).
1.4	2 June 2021	Revisions to the eCTD v4.0 Implementation Guide include the following change requests: additional validation rules (00580, 00590 and 00620) and removal of media type examples (00600).
1.5	24 May 2022	Revisions to the eCTD v4.0 Implementation Guide include the following change requests: Unique identifiers (00660), CoU Priority Numbers (00670), Document Reference (00690), Context of Use Code (00700), and Transition Mapping Message (00710). ***Note:*** *The Transition Mapping Message has been removed and replaced with a Forward Compatibility approach.*
1.6	21 May 2024	Revisions to the eCTD v4.0 Implementation Guide to include the following change requests: Validation rule to ensure documents are referenced by one CoU (00720); Validation rule to ensure the Context of Use identifier exists for suspended operations (00730); and Controlled Vocabulary Versioning (00750).

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NOTICE TO READERS

Sections of this document referencing the Health Level Seven ® International (HL7®) Version 3 Standard, Regulatory Product Submission Release 2 Normative are used with the publisher's permission. The HL7 Version 3 Standard 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 Electronic Common Technical Document (eCTD) v4.0 specification. The content is 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 Extensible Markup Language (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 is bold, italicised text in camel case, e.g., ***contextOfUse***
  - The XML samples are 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 capitalised.

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 Abbreviations and Terms

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

Abbreviation/Term	Definition
CEN	European Committee for Standardization
Class	Class is used in this document to qualify a base level element from the HL7 standard.
Context Group	Defines the context of a group of documents with the same Context of Use code and Keyword code combination. Previously known as "Document Group" in eCTD v4.0 Implementation Guide version 1.1.
Context of Use code and Keyword code combination	The combination includes both the code and code system for the Context of Use and Keyword in order to define the specific context group under which the documents are located.
Controlled vocabulary	A controlled vocabulary is an established list of standardised terminology for use in indexing and retrieval of information. [1]
Datatype	Datatype is used in this document to qualify elements and attributes that come from a datatype in the HL7 standard.
Document	Document is used in this document to identify 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.
Document Label	An abbreviated name for the document that may be assigned for each context of use.
eCTD	Electronic Common Technical Document

[1] Refer to ICH M2 Glossary of Terms and Abbreviations (https://www.ich.org/page/m2-recommendations-technical-references)

Abbreviation/Term	Definition
ESTRI	Electronic Standards for the Transfer of Regulatory Information Content may be found at: https://ich.org/page/electronic-standards-estri
EWG	Expert Working Group
Forward Compatibility	Refers to converting v3.2.2 content into v4.0 references to achieve life cycle and document reuse. This includes all xml sources index.xml, stf.xml, and regional xml.
Grouped Submission	A grouped submission is defined as a regulatory activity that impacts multiple dossiers, based on regulatory requirements. Implementation of grouped submission functionality may vary region to region.
Group Title	A sender-defined keyword that may be used to further organise content under a context group.
HL7	Health Level 7 – International Health Data Standards Development Organisation
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISO	International Organization for Standardization
IWG	Implementation Working Group
OID	Object Identifiers
Payload	The payload schema is the eCTD v4.0 base and it contains the elements in eCTD v4.0, including items from the Common Product Model and Common Message Element schema. It is organised with the following three elements in the structure: ***submissionUnit***, ***submission*** and ***application***.
RPS	Regulated Product Submission – HL7 standard
SDO	Standards Development Organisation
STF	Study Tagging File
URI	Uniform Resource Identifier
UUID	Universally Unique Identifiers
XML	Extensible Markup Language

XML Snippets

The following table 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***

Element's location in XML

```
<controlActProcess classCode="ACTN" moodCode="EVN">
    <subject typeCode="SUBJ">
        <submissionUnit>
            <id root="e6f34476-8288-43f2-a2ea-5860d19fcf32"/>
            <code code="regional_sub_unit_1" codeSystem="2.16.840.1.113883.3.989.x.x.x"/>
            <title value="Original Application- Indication: pain"/>
            <statusCode code="active"/>
            <component>
                <priorityNumber value="1000"/>
                <contextOfUse>
```

Refer to XML Color Legend for color usage.

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 9.2 of this document.

XML Elements Tables

A table has been provided for each element in the XML message. 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 not 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 harmonised for ICH and references to Regional/Module 1 Implementation Guides when the business rules are not harmonised.

Excluded Elements and/or Attributes: Identifies datatype elements and/or attributes that are part of the HL7 Regulated Product Submission standard and not included in the eCTD v4.0 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 HL7 Version 3 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.

This document describes converting an eCTD v3.2.2 application to eCTD v4.0 for Regions that allow forward compatibility. Refer to Regional/Module 1 Implementation Guides for specific use of this feature. The guidance for forward compatibility can be found in the following sections: Section 8 describes how to achieve forward compatibility; Section 9 incorporates specific instructions for life cycle and document reuse; and Section 12 includes rules that are required.

2.1 Business Case

Regulated Industry and Regulatory Authorities exchange information to address a variety of regulatory processes. The scope of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 are 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].

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

- **Document and Metadata life cycle** – the ability to manage the versions of documents and/or metadata.
- **Management of Context Groups** – the ability to group documents together based on nature of their use (e.g., components of clinical study reports)

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 Regulated Industry to Regulatory Authority 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.

In addition, the M2 EWG developed the Study Tagging File (STF) Specification. The STF was developed to identify the files associated with a study to provide a mechanism to organise the content within a particular study for Modules 4 and 5. When submitting a v3.2.2 message, the STF is required in the United States, is required in Canada if node extensions are not used, is not required in Europe, and is not allowed in Japan.

The implementation of the eCTD was done regionally and is described in the next section. Overall the eCTD has 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 worked on eCTD v4.0 through the HL7 process to ensure that the RPS message meets ICH requirements. Refer to Section 3.5 for more information on HL7. The RPS model meets both the ICH harmonised (Modules 2 – 5) requirements and the ICH regional requirements. RPS Release 2 passed in September 2014 as a HL7 version 3 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 that implemented eCTD v3.2.2 on or before the onset of eCTD v4.0 requirements gathering activities. Note - there are additional ICH regions that have implemented eCTD v3.2.2 since 2011.

3.2.1 Canada

In 2004, Health Canada began accepting regulatory activities filed in eCTD format as established by the ICH to address the increasing complexity and size of transactions and dossiers. Since 2009, the number of Regulatory Activities in eCTD Format has increased from 9.6% to 70%, and the number of boxes of

Regulatory Activities received by Health Canada in paper format has decreased by approximately 85%.

While Health Canada strongly recommends sponsors to use the eCTD to file electronic regulatory activities eligible to use this format, Health Canada is in the process of establishing next steps in order to mandate the use of the eCTD format for filing regulatory activities electronically in Canada.

3.2.2 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, The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). An alternative format, called Market Authorization by Network Submission and Evaluation (MANSEV) and based on Hypertext Markup Language, was developed in France, but was never implemented. These European formats and the work to harmonise at a European level were superseded by the ICH eCTD specification.

The ICH eCTD specification was adopted in Europe in 2002 (ICH Step 5). The number of submissions in this format has slowly increased over time. In 2007, due to the low level of adoption by Regulated Industry and Regulatory Authorities, 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 signature. The European Medicines Agency (EMA) started to accept electronic-only submissions with eCTD as the recommended format with no additional requirements for paper copies from 1st July 2008. It became mandatory to submit in eCTD format for the human Centralised Procedure on 1st of January 2010. eCTD format for new applications in the decentralised procedure became mandatory on 1 July 2015. Submission of new applications in mutual recognition procedure is mandatory from 1 January 2017.

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 needs to support in a broader sense.

3.2.3 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. As of December 2015, the majority of new drug applications in Japan are submitted as eCTD.

3.2.4 Switzerland

Swissmedic introduced eCTD v3.2.2 as exclusive electronic-only format in January 2010. The number of eCTDs submitted per year since then increased slowly and has reached approx. 15% by mid of 2015 based on all marketing authorisation applications including variations. Almost 100% of all new drug applications in Switzerland are submitted in eCTD format. Switzerland has no legal basis to mandate electronic submissions or even eCTD which is considered a main reason for the low use of eCTD. However, eCTD is the preferred format for all regulatory submissions to Swissmedic.

3.2.5 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 submissions 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 v3.2.2 has been the preferred format for electronic regulatory submissions to FDA.

On May 5, 2015, FDA published "Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" guidance. This guidance will require that marketing applications be submitted in the eCTD format starting in May 2017.

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 in 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 Standard Development Organisations (SDOs), initially International Organization for Standardization (ISO), HL7 and European Committee for Standardization (CEN), was drafted based on the "List of Critical Conditions for the SDO Message Standard Development Process". During 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.
An ICH Expert Working Group (EWG) and Implementation Working Group (IWG) was established 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 until Step 2 of the ICH process while also working through the HL7 standards development process to enhance the existing RPS Release 1 Standard. At this time point, the enhanced HL7 RPS Standard would be submitted 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, specifications, guidance and a set of tests to support the implementation of the expected ISO standard. This was planned as Step 3 and 4 activities of the ICH process to be in alignment with the publication of the ISO standard based on the HL7 Version 3 RPS Release 2 Normative Standard, and the ICH eCTD v4.0 Implementation Guide.

In 2015 ICH M8 published the Step 2 ICH eCTD v4.0 Implementation Guide for public consultation and the updates to this document are a result of those public comments. In September 2015 HL7 published the RPS Release 2 Normative Standard. Due to changes in the HL7 and ISO processes RPS Release 2 is not currently an ISO standard. The decision to publish this Step 4 implementation guide will allow regions to move forward with implementation and the acceptance of eCTD v4.0 submissions with the understanding that some regions will not be able to mandate eCTD v4.0 until there is an approved ISO RPS standard.

3.4 Advantages of eCTD v4.0

The advantage 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 standardisation 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:

Harmonised submission unit: In eCTD v4.0, the harmonised 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 is 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 supports the existing "new", "replace", and "delete" eCTD v3.2.2 life cycle operators; however, the support for the "append" operation has been removed from the eCTD v4.0 specification. If a submission has converted from v3.2.2 to v4.0, the sender will be able to life cycle any appended content along with its associated leaf when using the replace function in v4.0. See Section 9.2.7 Related Context of Use for additional information.

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, excipient, group title, etc.) without resubmitting the physical files or the Contexts of Use element.

Function of context 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 context groups includes the replacement for STFs in Modules 4 and 5 to organise multiple files relating to a single clinical study as noted in the 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 organise clinical study report documentation. In eCTD v4.0, the Context of Use code and Keyword code combination functions to create a group of documents in a specific context.

For additional information about the technical implementation, refer to Section 9.2.16.

3.5 Change Control

The eCTD v4.0 specification is based on the HL7 Version 3 RPS Release 2 Standard, which was developed in the external SDO, HL7, and with various stakeholders. Changes to the eCTD v4.0 schema[3] and resulting Implementation Guide will remain the responsibility of the ICH M8 EWG & 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

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

[4] This version of the Implementation Guide references the existing HL7 Version 3 RPS R2 Normative Standard and its change control processes.

[5] M8_eCTD_Concept_Paper.pdf available on the ICH website

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 given a disposition.

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 harmonise 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/or 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 (including the Modeling and Methodology, Infrastructure and Messaging, Vocabulary and the RPS Working Groups) are:

- Changes to the Reference Information Model
- Changes to the RPS Refined Message Information Models and/or referenced CMETs
- Changes to Controlled Vocabularies maintained by HL7
- Changes to Data Types used by RPS (Note: that this would also require changes to the ISO 21090 Data Type 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*[6]. 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:

- Object Identifiers (OIDs) and Universally Unique Identifiers (UUIDs) (summarised in Section 4.5)
- Data Types (summarised in Section 4.6)
- Regional/Module 1 Implementation Guides (summarised in Section 4.7)
- Files and Folders (detailed information provided in Section 5 and Section 11)
- Controlled Vocabulary (detailed information provided in Section 6)
- ICH eCTD v4.0 XML Schema (detailed information provided in Section 7)

[6] All ICH eCTD change control documentation can be found on the ich.org website.

- Forward Compatibility (detailed information provided in Section 8)
- eCTD v4.0 XML message (detailed information provided in Section 9)
- eCTD v4.0 Validation Rules (detailed information in Section 12)

Note: Refer to the ICH M8 ICH electronic Common Technical Document - eCTD v4.0 Website for a 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 in the message.

4.1 Files and Folders

The files (i.e., documents referenced in the XML message) will be sent in addition to the XML message. Each file will be organised 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 organise 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. The specific assignment of code system values can be found in the detailed description of OIDs and controlled vocabularies.

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 [7]. All other controlled vocabularies will be maintained by each Regulatory Authority or designated External organisation.

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

[7] Refer to the ICH electronic Common Technical Document - eCTD v4.0 website for additional information

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 organised by category and sub-categories in the table below. The schemas below are provided on the ICH electronic Common Technical Document - eCTD v4.0 website.

	Major Category	Schema Files	
1	**Core Schemas:** A common schema set for all HL7 Version 3 messages	datatypes-rX-cs.xsd hl7-r2_datatypes.xsd infrastructureRoot-r2.xsd NarrativeBlock.xsd voc-r2.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_MT700201UV02.xsd **Transmission**: MCCI_MT000100UV02.xsd
		Referenced Schema Files	
3	**Common Message Elements Schema[8]:** The CMETs referenced by the Common Product model or RPS Schemas	COCT_MT030203UV07.xsd COCT_MT040203UV09.xsd COCT_MT070000UV01.xsd COCT_MT090100UV01.xsd COCT_MT090108UV.xsd COCT_MT090300UV01.xsd COCT_MT090303UV01.xsd	COCT_MT150000UV02.xsd COCT_MT150003UV03.xsd COCT_MT150007UV.xsd COCT_MT710000UV07.xsd COCT_MT960000UV05.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 is one XML message created for a Submission Unit.

4.5 OIDs and UUIDs

There are two types of unique identifiers, OIDs and UUIDs. The subsections below provide additional information on how they are used by ICH eCTD v4.0.

[8] Note that Common Product Model schemas are requied for the complete RPS R2 schema. Refer to Module 1/Regional Implemenation Guides for additional information.

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) organisation(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 – 2.16.840.1.113883.3.989.2.2
- ich-estri-msg-stds-m8-ectd-code-lists – 2.16.840.1.113883.3.989.2.2.1
- ich-estri-msg-stds-m8-ectd-code-list-valueset-version – 2.16.840.1.113883.3.989.2.2.1.x.y

In ICH eCTD v4.0, the version OIDs will be used to provide the code system 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 organisations will have a registered OID. Note: The sender may determine whether or not to register OIDs for the sender-defined codes (Refer to Section 6.5 for additional information).

Note: The "x" value indicates the code system and "y" indicates the code system version.

4.5.2 Universally Unique Identifiers

A UUID is hexadecimal text in the form of 8-4-4-4-12 characters, i.e., text value includes 32 characters 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*** element) 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:

- Text – allows for any UTF-8 characters (includes Japanese characters).
- Alpha – allowing only alpha characters (e.g., A-Z) to be used
- Alpha Numeric – allowing alpha (A-Z) and numeric (0-9) to be used in a string. XML should follow W3C standards for alpha numeric values.

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[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

- 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.
- nullFlavors: these are used when required values need to be left blank. Null flavors are based on HL7 Messaging standard, and constraints are mentioned for each XML element. 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. The administrative information in the message 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 are available through the ICH M8 eCTD v4.0 website.

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***
- s***ubmission***
  - ***subject2.review***
    - ***subject1.manufacturedProduct***
    - ***holder.applicant***
    - ***author.territorialAuthority***
    - ***subject2.productCategory***
    - ***subject3.regulatoryStatus***
  - ***subject3.mode***
  - ***subject4.regulatoryReviewTime***
  - ***subject5.submissionGroup***
- ***componentOf2.categoryEvent***
  - ***component.categoryEvent***

Refer to 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 class elements are excluded from ICH eCTD v4.0, and the Applicant or Regulatory Authorities should follow the implementation notes for handling these elements in the XML message.

Elements in the Message Header:

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

Note to Implementers: *these elements should be included in the message and represented with self-closing tags, but should not include any values for the associated elements and attributes. Refer to Table 6 for the XML elements required by the schema. If these elements and associated elements and attributes are included in the XML message, they will be ignored by the receiver.*

Elements in the Payload Message:

- ***document***
  - ***referencedBy.Keyword***
- ***submission***
  - ***subject1.regulatoryStatus***

Note to Implementers: *If these elements and associated elements and attributes are included in the XML message, they will be ignored by the receiver.*

4.8 Excluded Business Processes

This document will not address any regional business processes. The regional business processes 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.
- **Grouped Submission –** may be handled differently across the regions due to the variation in regulatory processes.

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

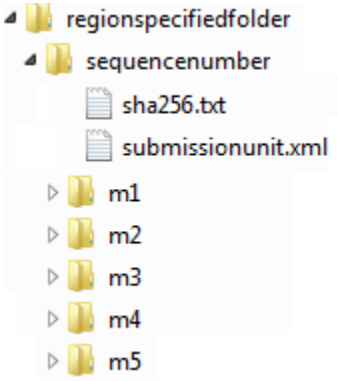
5. SUBMISSION CONTENTS, FOLDER AND FILE STRUCTURE

The folder and file structure specified for the document contents being transmitted along with the XML message should 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 1: Submission Unit Folder Structure



The *Region Specified Folder* will be determined by Region/Country and additional information can be found in the Regional/Module 1 Implementation Guides. Some regions may not utilize this folder.

The *Sequence Number Folder* should be the same for all regions and named with the "*sequencenumber*" 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:

- An ICH eCTD v4.0 XML Message for an individual Submission Unit, named "submissionunit.xml" is required. **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, refer to Section 9.1.
- A checksum of the XML eCTD instance (submissionunit.xml) should also be included in a text file and named "sha256.txt". The text file must be included in the sequence folder – i.e., in the same directory as the XML eCTD instance.
- 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. Refer to Sections 5.4 and 11. [11]
    - All files included in these folders should be accounted for in the XML message [12]

[11] Refer to Regional/Module 1 Implementation Guides for any exceptions to this rule.

[12] Refer to Regional/Module 1 Implementation Guides for any exceptions to this rule.

- Files previously sent do not need to be sent again [13]

Note to Implementers – the submissionunit.xml file replaces the previous v3.2.2 message files (i.e., index, regional and stf XML files).

Note to Implementers - the submission package should only contain folders when content is provided for the CTD module. The submission package should not contain empty folders.

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 file names should be unique within the folder. When files have specific naming requirements, additional folders may need to be added [14].
- 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. All alphanumeric characters are acceptable, and special characters should be limited to those in the table below.

Table 5: 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, including additional instructions for allowable characters of study data files.

[13] *Ibid.*

[14] *Ibid.*

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 sender's environment. If the path exceeds the 180 character limit or the regionally-defined limit, then folder and file names created by the applicant should be abbreviated.*
- File name extension = 3 or 4 characters

Consult Regional/Module 1 Implementation Guides for any additional constraints on the file or folder lengths.

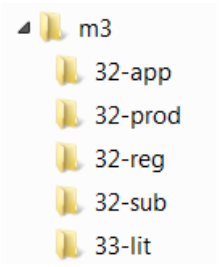
5.3 Pathname Conventions and Best Practices

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".

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 Figure 2: Sample Folder Hierarchy of Module 3.

Figure 2: Sample Folder Hierarchy of Module 3



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

Note: There should be no more than seven (7) levels of folders (i.e., nesting greater than 6 levels is not acceptable) within the Region Specified 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.

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 for any submission content, including study data.

Note: Refer to the Specification for Submission Formats for eCTD for additional information about ICH file specifications.

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:

- 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 Archive6611

A compressed archive is any collection of files that have been added to an archive and the archive has been compressed to minimise 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 for additional information about these files.

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 categorised below by the organisation 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: *The controlled vocabularies are provided both as genericode and spreadsheet files. The code lists controlled by ICH and Regions are available in the respective implementation packages.*
As of January 2024, the controlled vocabulary for ICH has been separated into its own package along with versioning. See Section 6.6 for additional information on CV Versioning.

The controlled vocabularies maintained by ICH and/or Regions will be under version control. The OID assigned to each code list will indicate its version number. When submitting vocabulary, the valid versions must be provided. Refer to the Section 3.5 for additional information regarding change control.

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. All ICH controlled vocabularies are provided in the genericode and spreadsheet files found in the ICH eCTD v4.0 Implementation Package.

- 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 (specifically Module 2 – 5).

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, etc.).

Consult Regional/Module 1 Implementation Guide to complete the list 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, document type, group title, etc.). Note: For the sender-defined value attributes of the keyword definitions – refer to Section 6.5. For keyword definition types, refer to the Controlled Vocabulary spreadsheet in the Implementation package.

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

- eCTD v4.0 – Media Types: Specifies the file format of specific documents. This additional information may be used by receiving implementations to enable special handling of the content.

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

6.2 Controlled Vocabularies specified Regionally

The controlled vocabularies specified by each Region for eCTD v4.0 are provided below. The ***codeSystem*** attribute provides the OID for each of the codes sets that 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 v4.0 – 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 – Media Types

Consult Regional/Module 1 Implementation Guide for a full list of allowable Media Types 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 v4.0 – Territorial Authority Role Codes

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

- eCTD v4.0 – 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 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 is not required in the XML message for any ***typeCode*** attribute. Note: These are fixed values and are provided in Section 9.2 of this document for each element that requires the ***typeCode*** to be specified.

- **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 status codes. Note: Status codes can only use the values provided by HL7 and specified by ICH. [15]

- **HL7 Update Mode Codes:** This vocabulary is provided in the HL7 Version 3 Standard for the ***updateMode*** attribute on certain elements within the XML message. These codes are required for the ***updateMode*** attributes. The schema has not been constrained and the allowable values are provided in this document for each element that requires the ***updateMode***. Refer to 9.2.2.3 for additional information about Update Mode.

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 business-friendly terms that are specified by Regulatory Authorities in the Regional/Module 1 Implementation Guides.*

6.4 Controlled Vocabulary specified by External Organisations

The controlled vocabulary specified by other organisations (i.e., not managed by ICH, Region or HL7) are provided below noting the responsible organisation, 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.

- **ISO Country Code – Two-letter Country Code:** This is the Country code that is specified in the ISO 3166-1 Standard.

6.5 Sender-defined Values

The topics in this section provide general guidance for assigning sender-defined values to XML elements in order to provide some consistency across applications within and across Regulated Industry. Any sender-defined values should be clear, concise and kept to a minimum number of characters to allow for a meaningful presentation of the information. Although there is no minimum character length for sender-defined values, the values may need to be truncated in viewing tools if they exceed display parameters (which may vary region to region).

6.5.1 Keyword Definitions

Vocabulary that has been sender-defined, specifically ***keywordDefinitions.value.item.code***, the message will require a ***code*** and ***codeSystem*** values. The applicant may use their own assignment of these values. In addition, the applicant may but does not need to follow the OID assignments noted in Section 4.5.1. If the OID assignments are used, either type of OID may be used as they are technically compatible.

[15] The allowable value set varies by element in the HL7 Version 3 RPS R2 Standard. For specifics of the ICH eCTD v4.0 Implementation, consult the genericode and spreadsheet files.

Receivers will use these values in the context of one application. Therefore, there should not be any collisions or issues with using the values for ***keyword*** codes within the application.

Note to Implementers: *There may be business scenarios that require the management of sender-defined vocabulary across applications (e.g., grouped submissions). It is recommended that keyword definitions be managed across applications to optimise their future use in each relevant Application as Context of Use keywords. Refer to Regional/Module 1 Implementation Guides for additional information.*

6.6 Controlled Vocabulary Implementation Package

This section outlines the contents of the controlled vocabulary for the code lists versioning and individual code values. The controlled vocabulary package includes the following:

- **Readme file** – includes the history and inventory of the controlled vocabulary's contents
- **eCTD v4.0 CV** – includes human-readable information for each code system
- **Genericode folder** – includes the machine-readable files for each code system

The human-readable and machine-readable code lists contain the same information.

Note to Implementers: *Refer to the ICH Controlled Vocabulary Implementation Package "Readme" file for a description of the file contents. Also refer to Regional/Module 1 Implementation Guides for additional information about regional code lists.*

6.6.1 Code Lists

This section outlines the information for each of the code lists. The code lists are provided in the controlled vocabulary package. Each of the code lists are are version controlled and include information regarding the use of each version of code lists.

Each code list includes the following key information which may be used to determine the support dates for the code system version:

- **Code System Name:** Name of Code System
- **Description:** Short description of the code list
- **XPATH**: Path in submissionunit.xml model to locate the element
- **Code System OID:** The value of the code system version
- **Start Date:** Date codelist/valueset begins support
- **Revision Notes:** Indicates the changes to the code list that have been made in the current version.

The code lists' versions are updated each time there is a change to the codes on the list. A code list can be used if it is valid.

6.6.1.1 *ICH Support Period*

The code lists have an ICH Support period. The ICH Support period has a start date and an end date. A code list may have one or more active versions at any given time.

Table 6: Sample Code List

Code System			ICH Support Period	
Type	**Code Set Name**	**Code System OID**	**Start Date**	**End Date**
ICH	ICH Code List 1	2.16.840.1.113883.3.989.2.2.1.X.1	n/a	n/a
		2.16.840.1.113883.3.989.2.2.1.X.2	2020-01-01	2022-01-01
		2.16.840.1.113883.3.989.2.2.1.X.3	2021-06-01	
		2.16.840.1.113883.3.989.2.2.1.X.4	2023-01-01	

The following sub-sections describe how to interpret the ICH Support Period – i.e., whether or not the code list is valid or retired from use as well as the lifecycle of the codes.

6.6.1.1.1 *Valid Code List*

A valid code list is indicated by the lack of an ICH Support Period End Date. More than one code system version can be supported at the same time. A code list may still be supported if the following changes have occurred between versions:

- No code change – but changes to text description, mappings or remarks/notes
- Addition of codes

The example in Table 6 shows two versions that are current, versions 3 and 4, and both may be used. New codes from version 4 in this example cannot be sent with the code system OID for version 3. The valid values should exist in the referenced code system.

6.6.1.1.2 *Retired Code List*

If a code list has been retired, it will have both an ICH Support Period Start and an End Date. A retired code list is not supported for use after its end date. A code list may be retired if the following changes have occurred between versions:

- Replacement codes
- Removal of codes
- If codes are used in a validation

The example in Table 6 shows a retired code list, version 2. The code list cannot be used as of the ICH Support End Date, 2022-01-01. If the code system OID for version 2 is submitted after the end date it will not be supported.

Note to Implementers: *Refer to the Validation Criteria for the use of ICH Support period. Also refer to Regional/Module 1 Implementation Guides for additional information.*

6.6.1.2 *Revision History*

The code lists also include a revision history to summarize the changes made for the current version only.

Note to Implementers: *Refer to the ICH Controlled Vocabulary Implementation Package "Readme" file for a detailed history of the controlled vocabulary. Refer to previous versions of the controlled vocabulary if details of previous changes are needed.*

6.6.2 Code Values

This section includes information about the code values for each code list. Code values may change over time. When code values change their status, operation and usage information will be provided in each code list.

The code values always have the following information available:

- **Code** – the code value identifier
- **Description** – a short name or explanation of the code value

The following information will be provided, if applicable:

- **References** – Refers to the guidance for use of the code value
- **Remarks/Notes** – Indicates any notes or remarks relevant to implementers
- **Status** – Indicates if the code is *active* and can be used or *retired* and no longer valid for use.
- **Operation** – Indicates whether the code was *added*, *replaced, removed,* or *no code change.*
- **Previous Valid Code(s)** – If the code is a replacement term, this will indicate the previous code(s)
- **Current Valid Code(s)** – If the code was retired, this will include the replacement code(s) for use
- **Last Valid Version** – Indicates the last version that a retired code was valid
- **Revision Notes** – Notes for implementers on how to handle this code after modification

Note to Implementers: *All context group validation rules apply. If any of the code values change, the life cycle for that content is broken. Content should be submitted as new with the new context group elements and previous content suspended if it is no longer relevant.*

The following sub-sections include additional information pertinent to the maintenance of code values within the code lists over time.

6.6.2.1 *Status*

The controlled vocabulary versioning is done at each code list (i.e., each tab on the spreadsheet or Genericode file), but within those code lists there are valid values for each version. A code value is either "Active" or "Retired". An "Active" code value is available for use as long as the code list is valid. A "Retired" code value is no longer available for use. It will include a value in the "Last Valid Version" columne. See Table 8 for an example of the Last Valid Version.

6.6.2.2 *Operations*

The code value is associated with one of the following options:

- **No Change to Code** includes changes to notes and/or mappings or updates between Controlled vocabulary and Genericode files
- **Added ("New")**: one or more codes are added to the code list. This should not force the retirement of the previous version if all changes were new codes.
- **Replaced:** one or more code values are replaced by one or more code values in the code list.
    - **Previous valid code(s)** – If the code value(s) is a replacement term, a reference to the previous code(s) will be included in this column

    - **Current valid code(s)** – If the code value(s) were replaced, a replacement code(s) will be included in this column
- **Removed:** one or more code values are removed from the code list and should no longer be used
- **None/Blank:** if the term existed prior to the current version, the operation field will be empty

Table 7 summarizes the potential status operations for the code values in a code list and any implications to the implementation of an internal or external controlled vocabuary.

Table 7: Code Value Operations

	No Code Change	Added	Replaced	Removed
Description	OID versioned without change to any of the code *i.e., just notes and/or mappings or updates between CV and Genericode files*	OID versioned with additional code values only	OID versioned with a **replacement** of value associated with one or more codes	OID versioned with a **removal** of a code value
Code List	May have multiple versions if this (notes/mappings update) is the only change in a code list	May have multiple versions if this (new code) is the only change in a code list	Indicates the valid implementation OIDs and timelines for implementation	Indicates the valid implementation OIDs and timelines for implementation
Code	The change that is made and status remains **"Active**	The addition is made, and status set to **"Active"**	The status of the code value is set to "**Retired"** The code value information includes the values of the current codes – i.e., replacement codes The replacement codes will point back to the retired code(s) Code list will be updated with an ICH Support end date.	The status of the code value is set to **"Retired"** Code list will be updated with an ICH Support period end date.

6.6.2.3 *Versioning Rules*

The following changes to code values within a code list may trigger the entire code list to be retired and assigned an ICH Support period end date for the previous code list version.

- The code list includes any removed values; or
- The replaced code value is to be used exclusively -- i.e., the retired code value should not be used under any circumstances.

When existing code values can be used in combination with the new ones, then retirement of the previous controlled vocabulary version is not necessary.

6.6.2.4 *Code List Example*

This section provides an example of changes to the code list. Table 8* illustrates the version 2 of a sample code list with the following revisions to the valid code values:

- **No Code Change:** Yellow (ich_color_2), Pure Blue (ich_color_3) are updated to add the hex color reference number
- **Add New:** Red-Orange (ich_color_7) and Orange (ich_color_8) are new code values
- **Replace:** Pure Red (ich_color_1) is replaced with Vivid Red (ich_color_5) and Strong Red (ich_color_6). Pure Red can no longer to be used after the ICH Support End Date of version 1
- **Remove:** Pink is removed, and can no longer be used after the ICH Support End Date of version 1

Table 8: Example of Code Values in Version 2 of Code List

Code	Description	Mappings/ Content*	Remarks/ Notes	Status	Operation	Previous Valid Code(s)	Current Valid Code(s)	Last Valid Version	Revision Notes
ich_color_1	Pure Red	-	-	Retired	Replaced	-	ich_color_5, ich_color_6	1	-
ich_color_5	Vivid Red	#ff0101	-	Active	Added	ich_code_1	-	-	-
ich_ color_6	Strong Red	#cd0000	-	Active	Added	ich_code_1	-	-	-
ich_color_7	Red-Orange	#ff4500	-	Active	Added	-	-	-	-
ich_color_8	Orange	#ffa500	-	Active	Added	-	-	-	-
ich_color_2	Yellow	#ffff00	-	Active	No code change	-	-	-	Reference added to hex color
ich_color_3	Pure Blue	#0000ff	-	Active	No code change	-	-	-	Reference added to hex color
ich_color_4	Pink	-	-	Retired	Removed	-	-	1	-

**Note: Included for illustrative purposes – i.e., the values are example and should not be submitted.*

7. ICH eCTD v4.0 XML Schema

7.1 Core Schema

The core schemas are 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 categorised 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.

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 9.1 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.

7.2.2 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 the required 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. FORWARD COMPATIBILITY

Forward compatibility should be used for any dossier that has v3.2.2 content where the application is being converted to a v4.0 message. Integration of v3.2.2 content with v4.0 content shall enable:

- Seamless presentation of v3.2.2 and v4.0 dossier content and information to users (i.e., builders/viewers/reviewers) with one tool to support publishing and viewing of complete dossier content comprising of v3.2.2 and v4.0 submissions.
- Continuous reference to v3.2.2 content
  - Enabling life cycle of active v3.2.2 content
  - Enabling document reuse of v3.2.2 content, including applications that have not converted to v4.0

- Once a v4.0 submission unit has been received for an application, all future sequences must be sent in v4.0 – i.e., a v3.2.2 message received after the initial v4.0 message is received will be rejected.

- Each Region will determine how to handle open regulatory activities when converting to v4.0 (i.e., if there are any special instructions).

Note to Implementers – these instructions should enable the forward compatibility once an application has moved to v4.0 messages. Refer to Regional/Module 1 Implementation Guide for specific details.

8.1 Considerations for Forward Compatibility

The instructions for submitting references to v3.2.2 content should align with the following conditions:

- Life cycle of submission content is only allowed for active (e.g., new, replace) leaf elements (i.e., content that is in the current view);
- When v3.2.2 content is replaced, it must follow v4.0 context group life cycle rules;
- When submitting the first eCTD v4.0 sequence to an eCTD v3.2.2 dossier the next available sequence number is submitted as a whole number. For example, if the last eCTD v3.2.2 message has a sequence number "0003", the first eCTD v4.0 submission unit will be sequence number "4";
- Validation rules apply to the submission unit with v3.2.2. references, and there are validations only relevant when forward compatibility is used in a submission unit; and
- When submitting v4.0 content that should be grouped with v3.2.2 content the keyword codes and values must match.

8.1.1 Uniquely Linking to v3.2.2 Leaf

Unique identifiers are required for v4.0 message objects – specifically Context of Use, Related Context of Use and Document Reference.

The **Leaf Reference** is composed of the following information:

- Application Identifier – regional identifier for application when referencing across applications for document reuse
- Sequence Number – the number assigned to the regulatory activity in v3.2.2 when the content was submitted (i.e., a four-digit value)
- XML Type – the v3.2.2 file type (e.g., ich or regional)[16]
- Leaf ID – the identifier submitted in v3.2.2 for the submission content being referenced

Therefore, when referencing v3.2.2 content, the following rules shall be followed:

- Use the v3.2.2 OID as the "namespace" in the ***id@root*** attribute to indicate that the content is unique to the previous application content
- Use the Leaf ID as the "identifier in said namespace" in the ***id@extension*** attribute to reference v3.2.2 leaf. The leaf ID should follow one of the following patterns:

[16] *Refer to ICH Controlled Vocabulary for a list of valid XML Types*

- Life Cycle references (within the same application):
  - sequenceNumber.xmlType.leafId (e.g.,0000.ich#NLAS57D17EB601C9EDCA)
- Document Reuse
  - Within the same application:
    - sequenceNumber.xmlType.leafId (e.g., 0000.ich#NLAS57D17EB601C9EDCA)
  - Across applications
    - Application Identifier with a Regionally assigned Application Type and Number: ApplicationTypeApplicationNumber.sequenceNumber.xmlType.leafId (e.g., nda123456.0000.ich#NLAS57D17EB601C9EDCA)
    - Application Identifier with a Regionally assigned Application Type and Number for Regional Content: ApplicationTypeApplicationNumber.sequenceNumber.xmlType.leafId (e.g., nda123456.0000.us-regional#NLAS57D17EB601C9EDCA)
    - Application Identifier with a Unique identifier (e.g., UUID): UUID.sequenceNumber.xmlType.leafId (e.g., 5f0e8436-e1df-4031-90d3-413deff109e5.0000.ich#NLAS57D17EB601C9EDCA)

Note to Implementers – Refer to Regional/Module 1 Implementation Guide for specific details on the expected values for Leaf Reference.

8.1.2 Special Forward Compatibility Considerations

Content from v3.2.2 may come from the index.xml, regional.xml or stf.xml files. When replacing ICH v3.2.2 content or submitting new v4.0 content that should be grouped with v3.2.2 content, the index.xml attribute values (e.g., manufacturer) and stf.xml values (e.g., study id title, file-tag) must match. The following table maps the content to v4.0 elements and attributes and expected usage

Table 9: Attribute Mappings

V3.2.2 Element/Attribute	Notes	V4.0 Element/Attribute	Notes
indication	These are index.xml attributes.	***keyword.code@code***	These are sender- defined keywords and keyword definitions need to be established before they are referenced in the keyword element,
substance			
manufacturer			
product-name			
dosageform			
excipient			

V3.2.2 Element/Attribute	Notes	V4.0 Element/Attribute	Notes
Study Id Study Title			
Study -id	This is the study identifier.	***keyword.code@code***	Study Id and Study Title is a single sender-defined v4.0 keyword (refer to 9.2.18.5.1). Keyword definitions need to be established before they are referenced in the keyword element. This value must match the study identifier provided in the study tagging file.
Title	This is the study title.		
Category	These include duration, route of administration, species, and type of control.	***keyword.code@code***	These include the keywords controlled by ICH and have individual value sets for duration, route of administration, species, and type of control.
Study Doc			
File-tag	This is the file-tag provided for the leaf.	***keyword.code@code***	This is the document type keywords controlled by ICH.
Property	This provides the site-id for a leaf element	***keyword.code@code***	This is the site-id keyword. The value is a sender-defined keyword definition.

The instructions for each of the forward compatibility features is included in Section 9.2, and Section 12.

9. 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.

9.1 Message Header

The message header information provides a set of elements that are needed to specify the sender and receiver as well as the version of the ICH and Regional/Module 1 Implementation Guides used to generate the message.

9.1.1 Sample XML

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

Table 10: Message Header XML Structure

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 PORP_IN000001UV.xsd">
  <id/>
  <creationTime/>
  <interactionId/>
  <processingCode/>
  <processingModeCode/>
  <acceptAckCode/>
  <receiver>
      <device classCode="DEV" determinerCode="INSTANCE">
          <id>
              <item root="" identifierName=""/>
          </id>
      </device>
  </receiver>
  <sender>
      <device classCode="DEV" determinerCode="INSTANCE">
          <id/>
      </device>
  </sender>
```

These elements should be represented with self-closing tags as shown here.

receiver.device.id (Section 9.1.2)

sender.device.id (Section 9.1.2)

9.1.2 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 reference the current interaction schema file i.e., xsi:schemaLocation="urn:hl7-org:v3 PORP_IN000001UV.xsd"
- ***receiver@typeCode*** has a fixed value of "RCV" and it does not need to be included in the message.
- ***receiver.device@classCode*** must have a value of "DEV"
- ***receiver.device@determinerCode*** must have a value of "INSTANCE"
- Include two ***id.item*** elements with the following information:
    - ***receiver.device.id.item@root*** should indicate the OID of the ICH eCTD v4.0 Implementation Guide or the Regional/Module 1 Implementation Guide used to create the message.
    - ***receiver.device.id.item@identifierName*** should indicate the version name of the ICH eCTD v4.0 Implementation Guide or the Regional/Module 1 Implementation Guide used to create the message. This value can be used to indicate the version number of the IG, but will not be used by the Regulatory Authority.
- ***sender@typeCode*** has a fixed value of "SND" and it does not need to be included in the message
- ***sender.device@classCode*** must have a value of "DEV"

- ***sender.device@determinerCode*** must have a value of "INSTANCE"

9.1.2.1 *XML Sample*

The following XML sample shows the content of the message header ***id*** element. The ***receiver.device.id*** element contains the IG versioning information:

```
<id/>
<creationTime/>
<interactionId/>
<processingCode/>
<processingModeCode/>
<acceptAckCode/>
<receiver>
    <device classCode="DEV" determinerCode="INSTANCE">
        <id>
          <item root="2.16.840.1.113883.3.989.2.2.1.11.4" identifierName="ICH eCTD v4.0 IG
v1.5"/>
          <item root="OID for Regional IG" identifierName="Regional/Module1 IG Version
Number"/>
        </id>
    </device>
</receiver>
<sender>
    <device classCode="DEV" determinerCode="INSTANCE">
        <id/>
    </device>
</sender>
```

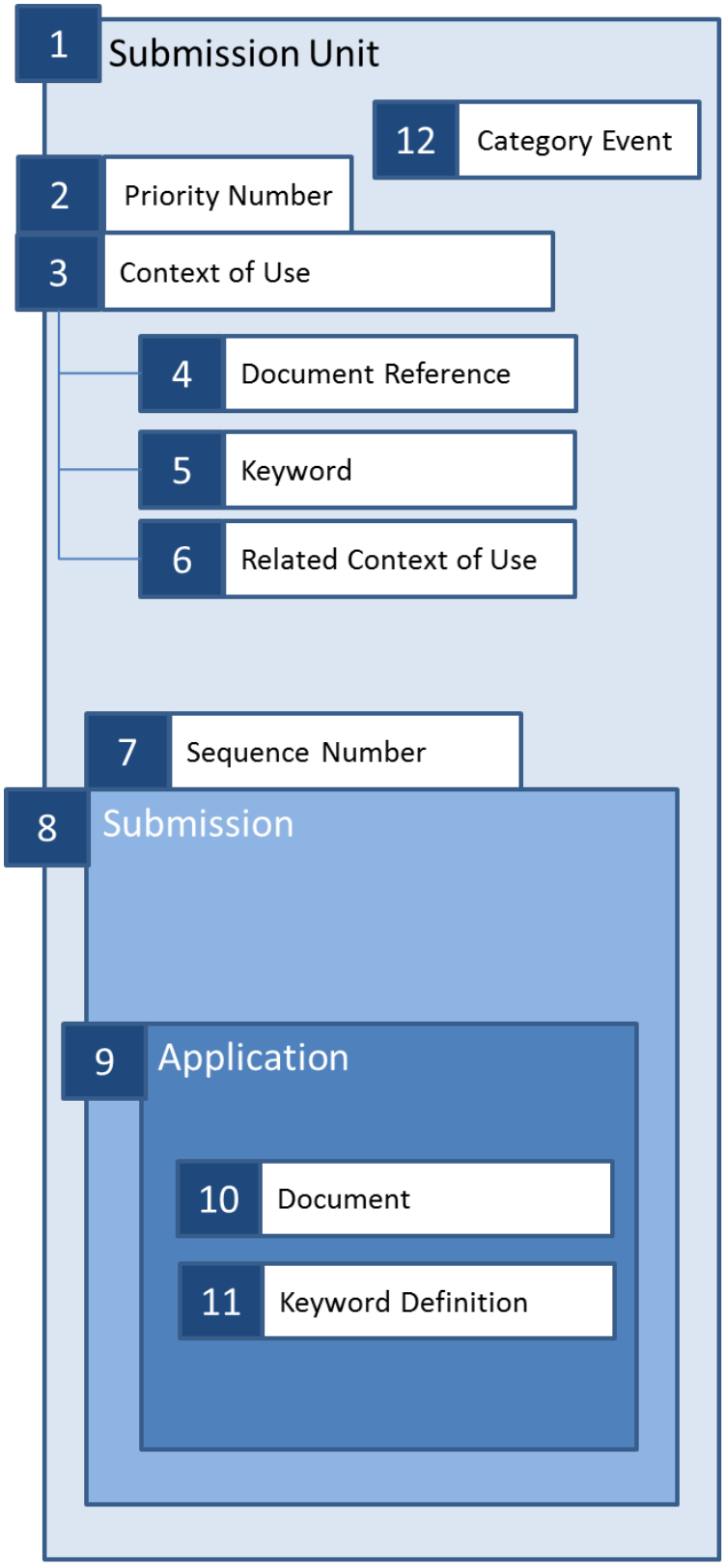
9.2 Payload Message

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

9.2.1 Concepts represented in the Payload Message

The following figure depicts the elements in the message and the relationships between them. Each of the elements represented in the figure are represented in the payload of the message.

Figure 3: Conceptual Model of Elements



Submission Unit - one eCTD Sequence 1

Priority Number – display order for Context of Use code and Keyword code combination 2

Context of Use – indicates the CTD Heading 3

Document Reference – indicates the document place under the CTD heading 4

Context of Use Keyword – additional information about the submission contents under the CTD heading 5

Related Context of Use – reference to the previously submitted content being replaced 6

Sequence Number – number assigned to the eCTD message 7

Submission - regulatory activity composed of one or more submission units 8

Application - includes one or more submissions and is used to identify the parent application in some regions 9

Document – includes additional information about the document and location in the folder hierarchy 10

Keyword Definition - defines sender-specified keywords 11

Category Event - provides additional information about the contents of the sequence 12

9.2.2 General Payload Considerations

The following considerations should be made for each of the elements in the payload message and described in Section 9.2.3.

9.2.2.1 *Required Elements*

The following attributes are required to start the payload of the XML message:

- ***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"

9.2.2.2 *Cardinality*

The schema for the XML does not constrain the data elements for the number of elements it may contain in the message. The guidelines in this document will indicate the conditions for sending elements in the message. If the cardinality indicates the element is optional (i.e., 0..1 or 0..*), there may be stated conditions which make them required. The cardinality assigned should be considered along with the stated conditions.

9.2.2.3 *Update Mode*

Specific data elements within the eCTD XML Message should include the ***updateMode*** to express a change to a previous submission unit. Each of the data elements that require ***updateMode*** will be indicated in the data element tables that allow update mode. It is important to know that the ***updateMode*** elements are marked optional because they are only to be used when sending an update at which time they are required. The update mode will be excluded for any data element that does not change after it is submitted.

9.2.3 XML Message Structure

The following table provides a breakdown of the eCTD v4.0 XML structure (i.e., the payload message) with all elements in the XML Schema. The table is organised with the following elements in the structure: ***controlActProcess***, ***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 number) or Regional/Module 1 Implementation Guides (not highlighted and noted as Regional) to identify the authoritative source of information for the element.

Table 11: v4.0 XML Message Structure

<table>
<tr><th colspan="2">XML Structure</th></tr>
<tr><td colspan="2">The eCTD v4.0 begins at the controlActProcess of the payload XML message. The required elements are noted above (Section 9.2.2.1), and precedes the submissionUnit element.</td></tr>
<tr><td colspan="2"><controlActProcess classCode="ACTN" moodCode="EVN">
<subject typeCode="SUBJ"></td></tr>
<tr><td colspan="2">The submissionUnit element contains the following Context of Use elements and their attributes:
• component.contextOfUse
o primaryInformationRecipient.TerritorialAuthority
o replacementOf.relatedContextOfUse
o derivedFrom.documentReference
o subjectOf.submissionReference
o referencedBy.keyword
Note: These elements are not included in this implementation guide. Refer to the Regional/Module1 Implementation Guides for additional information.</td></tr>
<tr><td><submissionUnit>
<id/>
<code/>
<title/>
<statusCode/>
<component>
<priorityNumber value=""/>
<contextOfUse>
<id/>
<code/>
<statusCode/>
<primaryInformationRecipient>
<territorialAuthority>
<governingAuthority>
<id/>
<name/>
</governingAuthority>
</territorialAuthority>
</primaryInformationRecipient>
<replacementOf typeCode="RPLC">
<relatedContextOfUse>
<id/>
</relatedContextOfUse>
</replacementOf>
<derivedFrom>
<documentReference>
<id/>
</documentReference>
</derivedFrom>
<subjectOf>
<submissionReference>
<id><item/></id>
</submissionReference></td><td>submissionUnit (Section 9.2.4)
Refer to <u>Regional/Module 1 Implementation Guides</u>

priorityNumber (Section 9.2.5)

contextOfUse (Section 9.2.6)

primaryInformationRecipient.territorialAuthority
Refer to <u>Regional/Module 1 Implementation Guides</u>

replacementOf.relatedContextOfUse (Section 9.2.7)

derivedFrom.documentReference (Section 9.2.8)

submissionReference
Refer to <u>Regional/Module 1 Implementation Guides</u></td></tr>
</table>

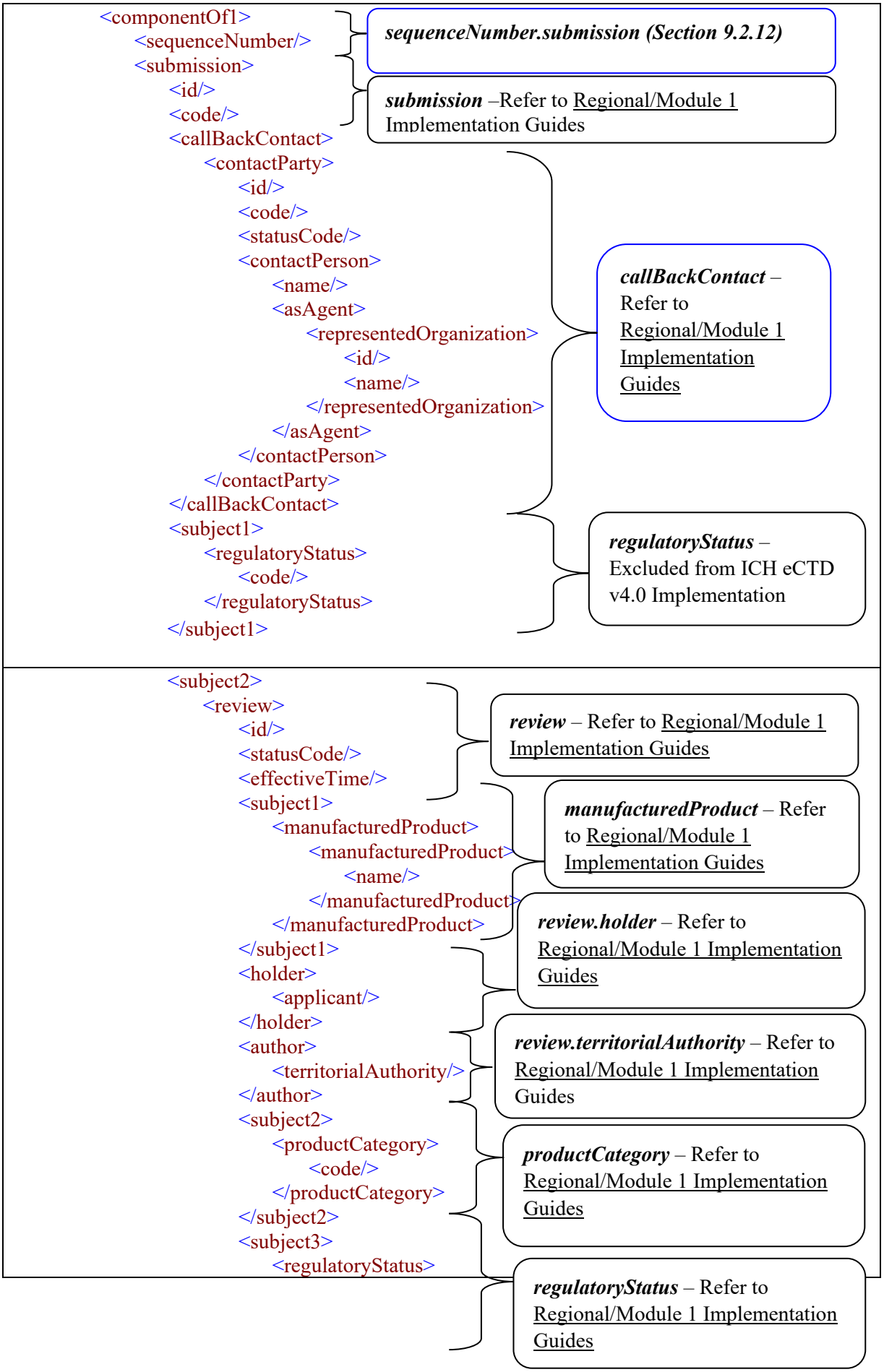
```
            </subjectOf>
            <referencedBy typeCode="REFR">
                <keyword>
                    <code/>
                </keyword>
            </referencedBy>
        </contextOfUse>
    </component>
```

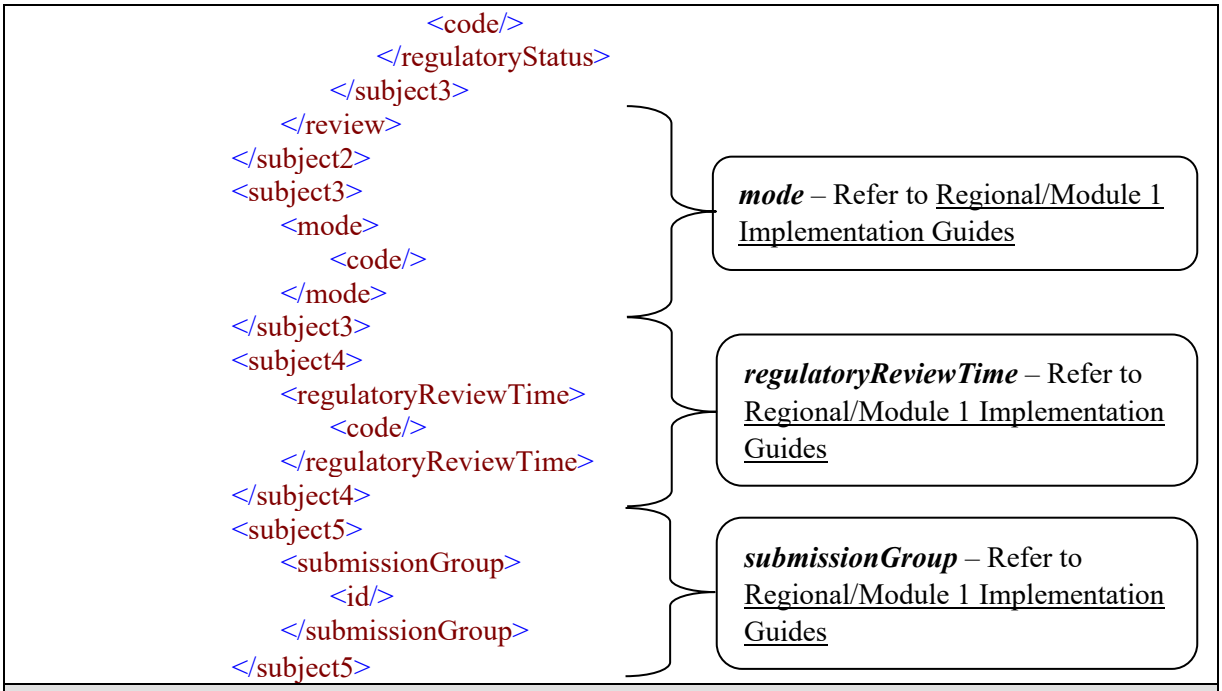
keyword (Section 9.2.9)

This section of the XML relates to specifying the ***submission*** element. The following elements may follow the Submission:

- ***sequenceNumber*** (included as an element of the relationship between ***submissionUnit*** and ***submission*** elements)
- ***callBackContact.contactParty***
- ***subject1.regulatoryStatus***
- ***subject2.review***
    - ***subject1.manufacturedProduct***
    - ***holder.applicant***
    - ***author.territorialAuthority***
    - ***subject2.productCategory***
    - ***subject3.regulatoryStatus***
- ***subject3.mode***
- ***subject4.regulatoryReviewTime***
- ***subject5.submissionGroup***

Note: These elements are not included in this implementation guide. Refer to the Regional/Module1 Implementation Guides for additional information.

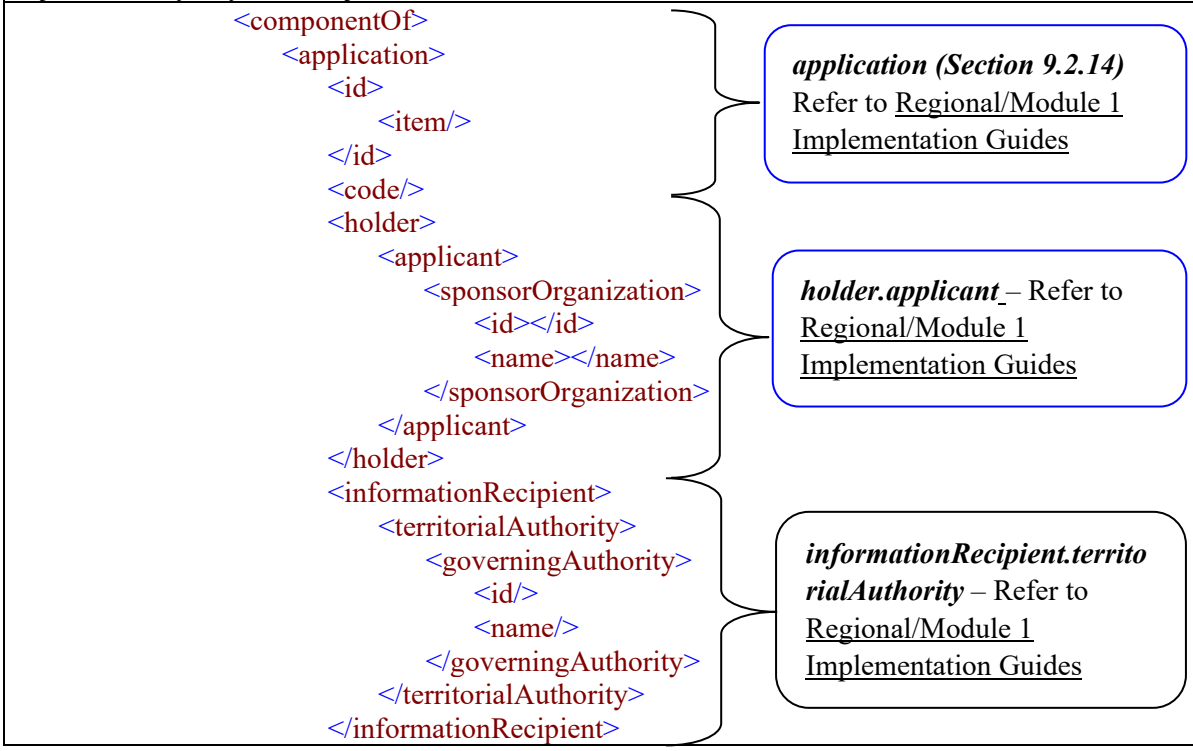

<componentOf1>
<sequenceNumber/>
<submission>
<id/>
<code/>
<callBackContact>
<contactParty>
<id/>
<code/>
<statusCode/>
<contactPerson>
<name/>
<asAgent>
<representedOrganization>
<id/>
<name/>
</representedOrganization>
</asAgent>
</contactPerson>
</contactParty>
</callBackContact>
<subject1>
<regulatoryStatus>
<code/>
</regulatoryStatus>
</subject1>
sequenceNumber.submission (Section 9.2.12)
submission –Refer to Regional/Module 1 Implementation Guides
callBackContact – Refer to Regional/Module 1 Implementation Guides
regulatoryStatus – Excluded from ICH eCTD v4.0 Implementation
<subject2>
<review>
<id/>
<statusCode/>
<effectiveTime/>
<subject1>
<manufacturedProduct>
<manufacturedProduct>
<name/>
</manufacturedProduct>
</manufacturedProduct>
</subject1>
<holder>
<applicant/>
</holder>
<author>
<territorialAuthority/>
</author>
<subject2>
<productCategory>
<code/>
</productCategory>
</subject2>
<subject3>
<regulatoryStatus>
review – Refer to Regional/Module 1 Implementation Guides
manufacturedProduct – Refer to Regional/Module 1 Implementation Guides
review.holder – Refer to Regional/Module 1 Implementation Guides
review.territorialAuthority – Refer to Regional/Module 1 Implementation Guides
productCategory – Refer to Regional/Module 1 Implementation Guides
regulatoryStatus – Refer to Regional/Module 1 Implementation Guides

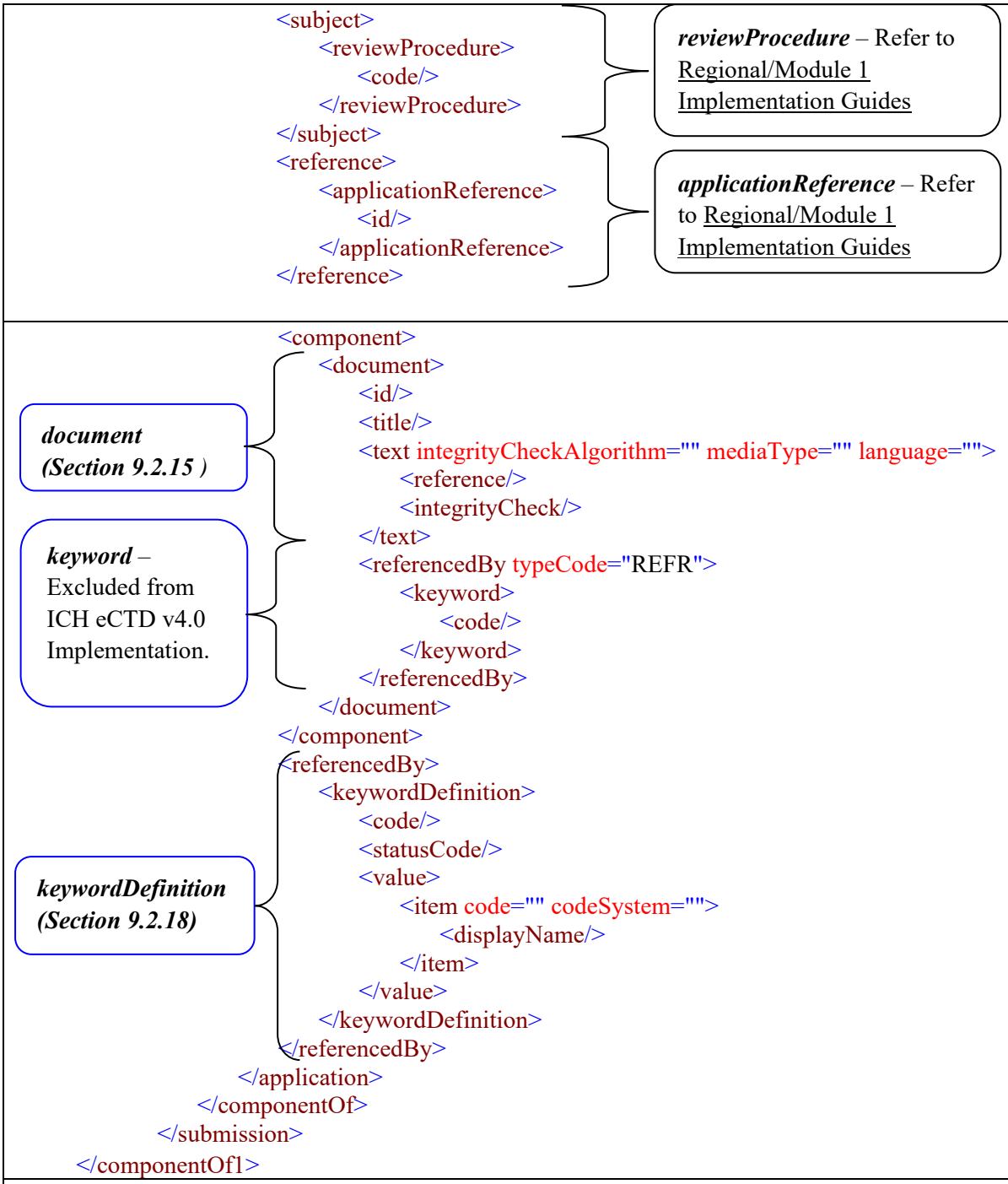


XML Structure

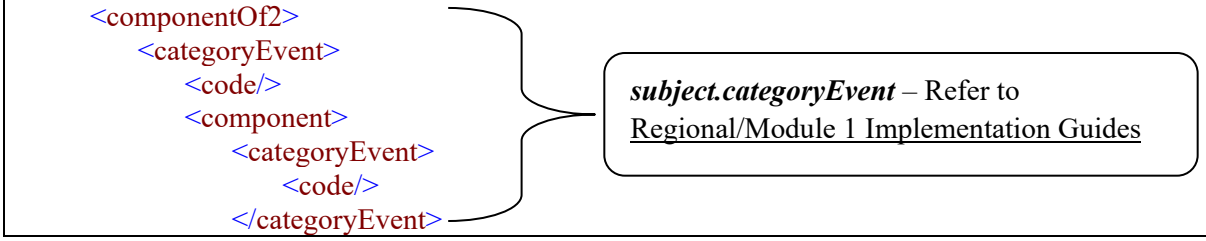
This section of the XML relates to the ***application*** element. The application section contains the following elements and their attributes:

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





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***).



```
            </component>
          </categoryEvent>
        </componentOf2>
      </submissionUnit>
    </subject>
  </controlActProcess>
</PORP_IN000001UV>
```

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

9.2.4 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: The **submissionUnit** element is applicable to all Modules. For region-specific requirements, Refer to the Regional/Module 1 Implementation Guide.*

9.2.4.1 *Location in XML*

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

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

Refer to Table 8: v4.0 XML Message Structure for more information.

9.2.4.2 *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.

9.2.4.2.1 *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	The ***root*** attribute of the ***id*** element provides a global unique identifier of the ***submissionUnit*** element.
Conformance	The ***id@root*** is a required attribute.			
Business Rules	The ***id@root*** should be unique for every ***submissionUnit*** element.			

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

9.2.4.2.2 ***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]	Text *e.g., regional_sub_unit_type_1* Refer to Regional/ Module 1 Implementation Guides	The ***code*** attribute 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	The ***codeSystem*** attribute provides a unique identifier that indicates the controlled vocabulary system. *This should be the OID registered for the code 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 datatype elements and attributes may not be required by eCTD v4.0: • ***code.displayName*** • ***code.originalText*** • ***code.translation*** • ***code.source*** • ***code@codeSystemName*** • ***code@codeSystemVersion*** • ***code@codingRationale*** • ***code@controlInformationExtension*** • ***code@controlInformationRoot*** • ***code@flavorId*** • ***code@id*** • ***code@nullFlavor*** • ***code@updateMode*** • ***code@validTimeHigh*** • ***code@validTimeLow*** • ***code@valueSet*** • ***code@valueSetVersion*** • ***code@xsi:type***			

9.2.4.2.3 ***submissionUnit.title***

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

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	The ***title*** is a sender-specified value that describes the purpose of the submission unit. This value is not specifically requested by Regulatory Authorities. Refer to Regional/Module 1 Implementation Guide for additional information.			
Excluded Elements and/or Attributes	The following datatype 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@charset*** • ***title@compression*** • ***title@controlInformationExtension*** • ***title@controlInformationRoot*** • ***title@flavorId*** • ***title@language*** • ***title@integrityCheckAlgorithm*** • ***title@nullFlavor*** • ***title@mediaType*** • ***title@updateMode*** • ***title@validTimeHigh*** • ***title@validTimeLow*** • ***title@xsi:type***			

9.2.4.2.4 ***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.

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
	code	[1..1]	Alpha *e.g., active, suspended* Refer to Regional/ Module 1 Implementation Guides	The ***code*** attribute of the ***statusCode*** element indicates the status of the submission unit.
Conformance	If the ***statusCode*** element is provided, the ***code*** attribute is required.			
Business Rules	The status codes sent in the message may only be active or suspended. Refer to Regional/Module 1 Implementation Guide for additional information and list of allowable values.			
Excluded Elements and/or Attributes	The following datatype elements and attributes may not be required by eCTD v4.0: • ***statusCode@controlInformationExtension*** • ***statusCode@controlInformationRoot*** • ***statusCode@flavorId*** • ***statusCode@nullFlavor*** • ***statusCode@updateMode*** • ***statusCode@validTimeHigh*** • ***statusCode@validTimeLow*** • ***statusCode@xsi:type***			

9.2.4.3 *Terminology*

All ICH controlled vocabularies are provided in the genericode and spreadsheet files.[17]

9.2.4.4 *Excluded Elements*

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

9.2.5 Priority Number for Context of Use

The priority number defines the order of elements in a Context Group. The ***priorityNumber*** element is always required to be provided. In cases where more than one Context of Use has the same ***contextOfUse.code@code*** and ***keyword.code@code*** combination, the ***priorityNumber*** will be used to display the elements.

9.2.5.1 *Location in XML*

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

[17] Final Implementation Terminology is provided on the ICH electronic Common Technical Document - eCTD v4.0 website.

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

Refer to Table 8: v4.0 XML Message Structure for more information.

9.2.5.2 *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 in 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 code and Keyword code combination.

9.2.5.2.1 *priorityNumber*

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
priorityNumber		[1..1]		This is the container element for the priority number and its value.
	value	[1..1]	Numeric *e.g., 1000,2000, 3000*	The ***value*** attribute of the ***priorityNumber*** element provides a whole number to be used for ordering the Context of Use within a context group.
	updateMode	[0..1]	Alpha *e.g., R for Replace*	The ***updateMode*** attribute provides the coded value to indicate if the ***priorityNumber*** has been changed for the Context of Use.
Conformance	The ***priorityNumber@value*** attribute is required.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	The priority number is required for each ***contextOfUse*** element. The ***priorityNumber*** is a positive integer. The values should begin with "1" and increment by whole numbers for the ***contextOfUse*** element with the same Context of Use code and Keyword code combination. The value should not be greater than "999999". It is recommended to start with "1000" and increment in intervals of 1000 (e.g., "2000", "3000", etc.) for the initial submission of a Context of Use sharing the same Context of Use code and Keyword code combination. This allows increments of ones, tens and hundreds to be used when reordering and/or inserting Context of Use. If priority numbers are no longer relevant (i.e., associated with replaced or suspended Context of Use elements), the sender may reassign the priority number to a new Context of Use code and Keyword code combination or when updating an existing Context of Use element. The priority number should not be duplicated within the same Context of Use code and Keyword code 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 Context of Use code and Keyword code 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 an existing Context of Use (i.e., ***updateMode***="R") along with a new Context of Use. 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 Context of Use is not being reordered with a new priority number value. Additional information is provided in Section 9.2.10.			

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

9.2.5.3 *Terminology*

There are no controlled vocabularies for this element.

9.2.5.4 *Excluded Elements*

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

9.2.6 Context of Use

The Context of Use defines the relationship between the table of contents heading (i.e., ***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** element 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@code*** and ***keyword.code@code*** combination.

9.2.6.1 *Location in XML*

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

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

Refer to Table 8: v4.0 XML Message Structure for more information.

9.2.6.2 *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:

- One-to-many ***contextOfUse*** elements can be sent in a ***submissionUnit.***
- Also see related Context of Use Keywords conditions.

9.2.6.2.1 *contextOfUse.id*

Element	Attribute	Cardinality	Value(s) Allowed	Description *Instructions*
id		[1..1]		This is the container element that organises the ***contextOfUse*** identifier.
	root	[1..1]	Valid UUID or OID 2.16.840.1.113883.3.989.2.2.1.13.1 *(with Forward Compatibility)*	The ***root*** attribute of the ***id*** element provides a global unique identifier or the v3.2.2 OID namespace of the ***contextOfUse*** element.
	extension	[0..1]	Leaf Reference *(with Forward Compatibility)*	The ***extension*** attribute of the ***id*** element provides a reference link to the v3.2.2 Leaf Reference and should only be used to suspend v3.2.2 content.
Conformance	The ***id@root*** is a required attribute. The ***id@extension*** attribute is required when the ***id@root*** attribute is 2.16.840.1.113883.3.989.2.2.1.13.1, its value must be a valid Leaf Reference (i.e., it exists in the receiver's system) and the ***ContextOfUse.statusCode@code*** is "suspended".			
Business Rules	The ***id@root*** should be unique for every ***contextOfUse*** submitted. For forward compatibility, if previous v3.2.2 content needs to be inactivated the OID and Leaf Reference shall be used, see Section 9.2.11.3.3 for examples.			

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

9.2.6.2.2 ***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]	Text *e.g., ich_3.2.p.2.3*	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.*
code.originalText	***value***	[0..1]	Text *e.g., 3.2.P.8.3-1*	The ***value*** attribute provides a document label that allows an abbreviated name for the document.
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 an "active" Context of Use. The ***code*** and ***originalText*** elements are not required if the ***contextOfUse.statusCode*** is inactivated (i.e., status code equals suspended) or when the associated ***priorityNumber*** is being updated. The ***originalText@value*** attribute is optional on all Context of Use elements to indicate an abbreviated name for the document referenced in the Context of Use. Note that the value will not be used for ordering purposes (see ***priorityNumber*** for ordering). Also, the ***value*** cannot be updated in a future sequence (note that the ***originalText@updateMode*** attribute is excluded from this implementation).			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following datatype elements and attributes may not be required by eCTD v4.0: • ***code.displayName*** • ***code.translation*** • ***code.source*** • ***code@codeSystemName*** • ***code@codeSystemVersion*** • ***code@codingRationale*** • ***code@controlInformationExtension*** • ***code@controlInformationRoot*** • ***code@flavorId*** • ***code@id*** • ***code@nullFlavor*** • ***code@updateMode*** • ***code@validTimeHigh*** • ***code@validTimeLow*** • ***code@valueSet*** • ***code@valueSetVersion*** • ***code@xsi:type*** • ***code.originalText.data*** • ***code.originalText.description*** • ***code.originalText.integrityCheck*** • ***code.originalText.reference*** • ***code.originalText.thumbnail*** • ***code.originalText.transtation*** • ***code.originalText.xml*** • ***code.originalText@charset*** • ***code.originalText@compression*** • ***code.originalText@controlInformationExtension*** • ***code.originalText@controlInformationRoot*** • ***code.originalText@ flavorId*** • ***code.originalText@integrityCheckAlgorithm*** • ***code.originalText@languange*** • ***code.originalText@mediaType*** • ***code.originalText@nullFlavor*** • ***code.originalText@updateMode*** • ***code.originalText@validTimeHigh*** • ***code.originalText@validTimeLow*** • ***code.originalText@xsi:type***			

9.2.6.2.3 *contextOfUse.statusCode*

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
statusCode		[1..1]		This is the container element that has a controlled vocabulary code that indicates the status of the Context of Use.
	code	[1..1]	Alpha *e.g., active, suspended*	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 Context of Use is specified.			
Business Rules	The ***statusCode@code*** attribute must always be sent in the message. Note: The status codes include an "obsolete" code that should not be sent in the XML message. The system will change the status of a Context of Use from active to obsolete once it has been replaced.			
Excluded Elements and/or Attributes	The following datatype elements and attributes may not be required by eCTD v4.0: • ***statusCode@controlInformationExtension*** • ***statusCode@controlInformationRoot*** • ***statusCode@flavorId*** • ***statusCode@nullFlavor*** • ***statusCode@updateMode*** • ***statusCode@validTimeHigh*** • ***statusCode@validTimeLow*** • ***statusCode@xsi:type***			

9.2.6.3 *Terminology*

All ICH controlled vocabularies are provided in the genericode and spreadsheet files. [18]

Codes may be further constrained by Regulatory Authorities, consult the appropriate Regional/Module 1 Implementation Guide.

9.2.6.4 *Excluded Elements*

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

9.2.7 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.

[18] Final Implementation Terminology is provided on the ICH electronic Common Technical Document - eCTD v4.0 website.

9.2.7.1 *Location in XML*

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

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

Refer to Table 8: v4.0 XML Message Structure for more information.

9.2.7.2 *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.***

9.2.7.2.1 *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 or OID 2.16.840.1.113883.3.989.2.2.1.13.1 *(with Forward Compatibility)*	The ***root*** attribute of the ***id*** element provides the global unique identifier or the v3.2.2 OID namespace for the ***relatedContextOfUse*** element being replaced.
	extension	[0..1]	Leaf Reference *(with Forward Compatibility)*	The ***extension*** attribute of the ***id*** element provides a reference link to the v3.2.2 Leaf Reference and should only be used when referencing v3.2.2 content.
Conformance	The ***id@root*** is a required attribute The ***id@extension*** is required when the ***id@root*** is 2.16.840.1.113883.3.989.2.2.1.13.1, and its value must be a valid Leaf Reference (i.e., it exists in the receiver's system).			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	One ***contextOfUse*** element can include one or more ***relatedContextOfUse*** elements. For forward compatibility, if previous v3.2.2 content needs to be replaced the OID and Leaf Reference shall be used, see Section 9.2.11.3.4 for examples.			
Excluded Elements and/or Attributes	The following datatype attributes may not be required by eCTD v4.0: • ***id@controlInformationExtension*** • ***id@controlInformationRoot*** • ***id@displayable*** • ***id@flavorId*** • ***id@identifierName*** • ***id@nullFlavor*** • ***id@reliabiity*** • ***id@scope*** • ***id@updateMode*** • ***id@validTimeHigh*** • ***id@validTimeLow*** • ***id@xsi:type***			

9.2.7.3 *Terminology*

All ICH controlled vocabularies are provided in the genericode and spreadsheet files. [19]

9.2.7.4 *Excluded Elements*

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

9.2.8 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 new Context of Use (i.e., with active status code) must reference a document.

9.2.8.1 *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 8: v4.0 XML Message Structure for more information.

[19] Final Implementation Terminology is provided on the ICH electronic Common Technical Document - eCTD v4.0 website.

9.2.8.2 *XML Elements*

The following table provides a complete set of XML elements and attributes required for the ***documentReference*** 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 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.*** Note: The document reference is not necessary when suspending a Context of Use element.
- For a ***contextOfUse.statusCode@code*** = active – the ***documentReference*** element is required.
- For a ***contextOfUse.statusCode@code*** = suspended – the ***documentReference*** element should not be provided.

9.2.8.2.1 *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 or OID 2.16.840.1.113883.3.989.2.2.1.13.1 *(with Forward Compatibility)*	The ***root*** attribute provides a global unique identifier or the v3.2.2 OID namespace of the ***document*** element being referenced.
	extension	[0..1]	Leaf Reference *(with Forward Compatibility)*	The ***extension*** attribute of the ***id*** element provides a reference link to the v3.2.2 Leaf Reference and should only be used when referencing v3.2.2 content.
Conformance	The ***id@root*** attribute is required if the ***documentReference*** element is provided. The ***id@extension*** is required when the ***id@root*** is 2.16.840.1.113883.3.989.2.2.1.13.1, and its value must be a valid Leaf Reference (i.e., it exists in the receiver's system).			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	The ***id@root*** is a reference to a document sent in the submission unit or a previously submitted submission unit. For forward compatibility, the document referenced from a v3.2.2 will reuse its existing metadata for the document without changes. See Section 9.2.17.1 for how to handle document reuse of v3.2.2 content. Refer to applicable Regional/Module 1 Implementation Guide for specifics on document retention of regulatory submissions.			
Excluded Elements and/or Attributes	The following datatype attributes may not be required by eCTD v4.0: • ***id@controlInformationExtension*** • ***id@controlInformationRoot*** • ***id@displayable*** • ***id@flavorId*** • ***id@identifierName*** • ***id@nullFlavor*** • ***id@reliabiity*** • ***id@scope*** • ***id@updateMode*** • ***id@validTimeHigh*** • ***id@validTimeLow*** • ***id@xsi:type***			

9.2.9 Context of Use 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***.

9.2.9.1 *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 8: v4.0 XML Message Structure for more information.

9.2.9.2 *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.
- On each Context of Use element, a valid Keyword Type shall only be used once.
- Required keywords for a Context of Use code attribute must be included.
- The Keyword Type must be valid for the Context of Use heading.
- Consult Regional/Module 1 Implementation Guides for specific types of Keywords that should be used with ***contextOfUse*** elements.

9.2.9.2.1 ***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]	Text *e.g., ich_route_1, MANU001 or MFR_001 for Manufacture Site*	The ***code*** attribute identifies the code value for the keyword.
	codeSystem	[1..1]	Text *e.g., OID value or Sender-defined text*	The ***codeSystem*** attribute provides a unique identifier that indicates the controlled vocabulary system.
Conformance	The ***code*** and ***codeSystem*** attributes are required. A keyword can only have one code.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	A keyword coming from a controlled vocabulary must provide an OID for the ***codeSystem*** value. A keyword that was sender-defined must provide an OID or text value assigned by the sender. The display name for the ***code*** needs to be retrieved from the corresponding code system. For forward compatibility, when replacing v3.2.2 content keywords must match the attributes, node extensions, file-tags, property or categories previously submitted in v3.2.2. All existing values shall be provided regardless of keyword type – i.e., now part of a controlled vocabulary or a keyword definition. If a node-extension was previously allowed, the group title keyword definition should be used to send the same value. If multiple node extensions were provided on the same heading or nested, the values should be concatenated into one group title keyword definition. In addition, refer to Regional/Module 1 Implementation Guide for Module 1 Context of Use vocabulary that may be replacements for node-extensions. See mappings in Section 8.3 for specifics.			
Excluded Elements and/or Attributes	The following datatype elements and attributes may not be required by eCTD v4.0: • ***code.displayName*** • ***code.originalText*** • ***code.translation*** • ***code.source*** • ***code@codeSystemName*** • ***code@codeSystemVersion*** • ***code@codingRationale*** • ***code@controlInformationExtension*** • ***code@controlInformationRoot*** • ***code@flavorId*** • ***code@id*** • ***code@nullFlavor*** • ***code@updateMode*** • ***code@validTimeLow*** • ***code@validTimeHigh*** • ***code@valueSet*** • ***code@valueSetVersion*** • ***code@xsi:type***			

9.2.9.3 *Terminology*

All ICH controlled vocabularies are provided in the genericode and spreadsheet files. [20]

9.2.9.4 *Excluded Elements*

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

9.2.10 Considerations for Keywords

There are special considerations for the usage of some keyword types. These considerations are outlined below.

9.2.10.1 *Keyword Type: Study Group Order*

If the sender would like to specify a numerical value to order study id_study title (i.e. studies) within context group, the keyword type of "study group order" shall be used. The use of this keyword type should also follow these rules:

- The study group order keyword should only be used when there is a study id_study title keyword in the context group as defined in the ICH Context of Use controlled vocabulary.
- If the study group order type keyword is included without the study id_study title keyword it will be ignored by the receiver.

Refer to Section 9.2.18.5.1 for information about the assignment of keyword definition values for this keyword type.

9.2.10.2 *Keyword Type: Group Title*

If the sender would like to specify additional organisation of the context group at the lowest heading level, the group title is an optional keyword type for this use. Refer to Section 9.2.16.1 for information about the assignment of keyword definition values for this keyword type.

9.2.11 XML SAMPLES: Context of Use

9.2.11.1 *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 one ***priorityNumber*** element.

```
<component>
    <priorityNumber value="1000"/>
    <contextOfUse>
        <id root="1f080afd-f5d4-4cec-8d09-2bf0ea6bec66"/>
        <!—Original Text is an optional element of the Context of Use.-->
            <code code="ich_3.2.s.2.3" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1">
            <originalText value="3.2.s.2.3-1"/>
        </code>
        <statusCode code="active"/>
```

[20] Final Implementation Terminology is provided on the ICH electronic Common Technical Document - eCTD v4.0 website.

```
            …
            [Additional information may appear after the addition of the contextOfUse –
            primaryInformationRecipient]
            …
        <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. Refer to Regional/Module 1 Implementation Guide for
            this element.]
            …
        <referencedBy typeCode="REFR">
            <keyword>
                <code code="MANU001" codeSystem="2.16.840.1.113883.3"/>
            </keyword>
        </referencedBy>
        <referencedBy typeCode="REFR">
            <keyword>
                <code code="SUB001" codeSystem="2.16.840.1.113883.3"/>
            </keyword>
        </referencedBy>
    </contextOfUse>
</component>
```

All Context of Use keywords are shown for illustration purposes only. Refer to the controlled vocabulary and ICH M4 Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use files for the allowable combinations.

*Note to readers: In the example above the **originalText** attribute of the Context of Use provides an additional document label (i.e., an abbreviated name for the document) that may be used by the receiving system's users as a reference value for ease of use for review activities. Refer to Regional/Module 1 Implementation Guides for specific usage.*

Refer to XML Color Legend for color usage.

The ***contextOfUse*** 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@code*** and

keyword.code@code combination. The XML Sample below depicts an example of how priority number is used within a Context Group.

```
<component>
    <priorityNumber value="1000"/>
    <contextOfUse>
        <id root="27c069e1-8fec-4b07-907e-cf691543cf66"/>
        <code code="ich_3.2.s.2.3" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <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="2.16.840.1.113883.3"/>
            </keyword>
        </referencedBy>
        <referencedBy typeCode="REFR">
            <keyword>
                <code code="SUB001" codeSystem="2.16.840.1.113883.3"/>
            </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="2.16.840.1.113883.3.989.2.2.1.1.1"/>
            <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="2.16.840.1.113883.3"/>
                </keyword>
            </referencedBy>
            <referencedBy typeCode="REFR">
                <keyword>
                    <code code="SUB001" codeSystem="2.16.840.1.113883.3"/>
                </keyword>
```

```
            </referencedBy>
        </contextOfUse>
</component>
```

All Context of Use keywords are shown for illustration purposes only. Refer to the controlled vocabulary and ICH M4 Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use files for the allowable combinations.

Refer to XML Color Legend for color usage.

9.2.11.2 *XML Sample: Study Group Order Keyword*

The following is an example of the XML for the optional keyword type of study group order to illustrate how it may be used to assign a study group order. Note that the priority number will still be used to order the contents within a context group.

```
    <component>
        <priorityNumber value="2000"/>
            <contextOfUse>
                <id root="3b60de11-5277-4a62-be4a-6ac87e046e1b"/>
                <code code="ich_4.2.3.1" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
                <statusCode code="active"/>
                <derivedFrom>
                    <documentReference>
                        <id root="be916755-a4bc-454a-b1c1-b1c0b2cf76cd"/>
                    </documentReference>
                </derivedFrom>
                <referencedBy typeCode="REFR">
                    <keyword>
                        <code code="STDY1-TITLE1" codeSystem="2.16.840.1.113883.3.989"/>
                    </keyword>
                </referencedBy>
                <referencedBy typeCode="REFR">
                    <keyword>
                        <code code="ich_document_type_4"
codeSystem="2.16.840.1.113883.3.989.2.2.1.3.2"/>
                    </keyword>
                </referencedBy>
                <referencedBy typeCode="REFR">
                    <keyword>
                        <code code="ich_species_2" codeSystem="2.16.840.1.113883.3.989.2.2.1.7.1"/>
                    </keyword>
                </referencedBy>
                <!—Study Group Order is an optional keyword type .-->
                <referencedBy typeCode="REFR">
                    <keyword>
```

```
                    <code code="ich_study_group_order_1"
codeSystem="2.16.840.1.113883.3.989.2.2.1.12.1"/>
                </keyword>
            </referencedBy>
            <referencedBy typeCode="REFR">
                <keyword>
                    <code code="ich_route_1" codeSystem="2.16.840.1.113883.3.989.2.2.1.6.1"/>
                </keyword>
            </contextOfUse>
        </component>
```

All Context of Use keywords are shown for illustration purposes only. Refer to the controlled vocabulary and ICH M4 Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use files for the allowable combinations.

Note to the reader: In the example above the keyword type for Study Group Order is used to help further organise the Study information. This value will not replace the use of the priority number.

Refer to XML Color Legend for color usage.

9.2.11.3 *Considerations for 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 harmonised:

- When replacing a Context of Use, the two instances must have the same Context of Use code and Keyword code combination (i.e., this will allow the submission content 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***:

- **Replacing the Context of Use:** To provide a new ***contextOfUse***, with a different document or previously referenced document in the ***documentReference*** element.
- **Removal (Suspend) 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.
- **New Keyword(s):** A Context of Use that needs changes to the keywords (i.e., change in Context of Use code and Keyword code combination) would use the suspension of a Context of Use and submission of a new Context of Use. If the sender is only changing the keyword definition's display name, the code value will remain the same and is not considered a new keyword.

9.2.11.3.1 *Inserting New Context of Use Elements*

If a ***submissionUnit*** includes components with the same ***contextOfUse*** code and ***keyword*** code, a priority must 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="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <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="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <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@code*** and ***keyword.code@code*** combination as in the previous examples. As content is added over time to the same heading, the priority number will indicate the placement among the existing content. 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_3.3" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <statusCode code="active"/>
        <derivedFrom>
            <!—Literature Reference Document #3-->
            <documentReference>
                <id root="1982f2bf-bd82-45c6-83d7-8838598c971f"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

Refer to XML Color Legend for color usage.

9.2.11.3.2 ***Reordering Context of Use***

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

Reordering may also need to occur when a new Context of Use needs to be inserted between existing Context of Use. 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.
- If a component needs to be reordered, the ***contextOfUse.priorityNumber@updateMode*** is used to indicate the only change to the Context of Use is to the placement of the content.

The following example is the basic reordering of the previous context of use that was sent in the incorrect order. Note that any reordering of the Context of Use does not include the ***contextOfUse.code***, ***documentReference.id*** and ***keyword.code*** elements. The content will be placed in the corrected order (e.g., previously submitted as priority number 5000). Note: It is recommended that the applicant does not send a submission unit just to reorder ***contextOfUse*** elements.

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

The example below shows the reordering of the content after those with lower priority numbers in the listing of content with the same Context of Use with Keywords (e.g., previously submitted in m3.2.s.2.3 with a keyword for manufacturer and substance).

```
<component>
```

```
        <priorityNumber value="1500" updateMode="R"/>
        <contextOfUse>
            <id root="1f080afd-f5d4-4cec-8d09-2bf0ea6bec66"/>
            <statusCode code="active"/>
        </contextOfUse>
    </component>
```

Refer to XML Color Legend for color usage.

9.2.11.3.3 *Removing / Suspending 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>
```

In the case of Forward Compatibility, the Context of Use id references the Leaf Reference of the previous v3.2.2 content.

```
<component>
    <priorityNumber value="1000"/>
    <contextOfUse>
        <id root="2.16.840.1.113883.3.989.2.2.1.13.1" extension="0000.ich#NLAS57D17EB601C9EDCA"/>
        <statusCode code="suspended"/>
    </contextOfUse>
</component>
```

For Applications that have converted to v4.0, content may be suspended if it is no longer relevant, or needs to be placed under the new v4.0 Context of Use code and Keyword code combination. See Section 9.2.16.4 for additional details.

Refer to XML Color Legend for color usage.

9.2.11.3.4 *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:

- The submission contents (i.e., the document being referenced) have changed
- The previous suspended submission content needs to be resubmitted.*

*If the content needs to be resubmitted, only a new Context of Use will be sent in the message, the document id should be referenced and the physical file does not need to be resubmitted.

The new ***contextOfUse*** element will have a new unique identifier and 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 ***relatedContextOfUse*** will be marked as "obsolete" by the system (Refer to Section 9.2.7 for additional information). Note: An obsolete Context of Use cannot be replaced after its initial replacement (i.e., a Context of Use marked obsolete should not be referenced in a ***relatedContextofUse*** element). 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. The priority numbers may be reassigned or new (whether the number is before or after existing values).

```
<component >
    <priorityNumber value="1000"/>
    <contextOfUse>
        <id root="b205bb7c-a222-4557-a954-0363dc122ca8"/>
        <code code="ich_2.7.1" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <statusCode code="active"/>
        <replacementOf typeCode="RPLC">
            <relatedContextOfUse>
                <id root="78b2f721-25f0-474d-914b-5efb026cc7f7"/>
            </relatedContextOfUse>
        </replacementOf>
        <derivedFrom>
            <documentReference>
                <id root="6ee97feb-8cd1-4991-8c38-002f16102fca"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

Note: The example above is reassigning the priority number used in the previous context of use – i.e., as referenced by the ***relatedContextOfUse*** element.

In the case of Forward Compatibility, the related Context of Use references the Leaf ID of the previous v3.2.2 content.

```
<component>
```

```
    <priorityNumber value="3000"/>
    <contextOfUse>
        <id root="1fc6b866-cd74-4d96-8b10-c5d2578d0a3e"/>
        <code code="ich_3.2.p.1" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.3"/>
        <statusCode code="active"/>
        <replacementOf typeCode="RPLC">
            <relatedContextOfUse>
                <id root="2.16.840.1.113883.3.989.2.2.1.13.1"
                extension="0000.ich#NLAS57D17EB601C9EDCA"/>
            </relatedContextOfUse>
        </replacementOf>
        <derivedFrom>
            <documentReference>
                <id root="0bfd53f6-76de-4b62-8cf2-cc9b57d2f375"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

For Applications that have converted to v4.0, content may only be replaced if it exists under the same Context of Use code and Keyword code combination. Refer to Section 9.2.16.4 for additional details.

Refer to XML Color Legend for color usage.

9.2.12 Sequence Number

The ***sequenceNumber@value*** is typically, but not always 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. The applicant's sequence number practices will remain the same in v4.0.

Implementation Note: *Refer to Regional/Module 1 Implementation Guide for sequence numbers issued as part of two-way communication. They will have an independent series of values that will only be differentiated by the party sending the message (i.e., the values are not consecutive between the two parties).*

9.2.12.1 *Location in XML*

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

- ***controlActProcess*** >> ***subject*** >> ***submissionUnit >> componentOf1 >> sequenceNumber***

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

Refer to Table 8: v4.0 XML Message Structure for more information.

9.2.12.2 *XML Elements*

The following table provides a complete set of XML elements and attributes required for the ***componentOf1.sequenceNumber*** 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.*

9.2.12.2.1 *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	The ***sequenceNumber@value*** attribute is required.			
Business Rules	The ***sequenceNumber*** is a positive integer. The values should begin with "1" and increment by whole numbers. The value should not be greater than "999999".			
Excluded Elements and/or Attributes	The following datatype elements and attributes may not be required by eCTD v4.0: • ***sequenceNumber.expression*** • ***sequenceNumber.originalText*** • ***sequenceNumber.uncertainty*** • ***sequenceNumber.uncertainRange*** • ***sequenceNumber@controlInformationExtension*** • ***sequenceNumber@controlInformationRoot*** • ***sequenceNumber@flavorId*** • ***sequenceNumber@nullFlavor*** • ***sequenceNumber@uncertaintyType*** • ***sequenceNumber@updateMode*** • ***sequenceNumber@validTimeHigh*** • ***sequenceNumber@validTimeLow*** • ***sequenceNumber@xsi:type***			

9.2.12.3 *Terminology*

There are no controlled vocabularies for this element.

9.2.13 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="regional_sub_unit_type_1" codeSystem="2.16.840.1.113883.3.989.x.x.x"/>
        <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 it will
                come after 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–
                component or componentOf1 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 9.2.11 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>
```

Refer to 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.

9.2.14 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.

9.2.14.1 *Location in XML*

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

- ***controlActProcess>> subject>> submissionUnit>>componentOf1>>submission>> componentOf>>application***

Refer to Table 8: v4.0 XML Message Structure for more information.

9.2.14.2 *XML Elements*

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

```
…
[This XML section will repeat for each application element.  A submission element is a component of an application element]
…
<componentOf>
   <application>
      <id>
         <item root="2.16.840.1.113883.3.989.5.1.2.2.1.16.1" extension="987654"/>
      …
      <!--Additional item elements can be added here-->
      …
      </id>
      <code code="us_application_type_1" codeSystem="2.16.840.1.113883.3.989.5.1.2.2.1.1"/>
            …
            [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>
```

Refer to XML Color Legend for color usage.

Refer to Regional/Module 1 Implementation Guide for assignment of application identifier.

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.*

9.2.14.2.1 ***application.id***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
id		[1..1]		This is the container element for the identifier items.
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 OID or UUID	The ***root*** attribute of the ***id.item*** element provides a global unique identifier for the ***application*** element.
	extension	[0..1]	Text *e.g., 123456 (Sample U.S. NDA value)*	The ***extension*** attribute of the ***id.item*** 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	Refer to Regional/Module 1 Implementation Guide for assignment of application number and appropriate ***id.item@root*** value as an OID or UUID. If the ***application.id.item@root*** includes the OID namespace, the value in ***application.id.item@extension*** should follow the regional requirements. Refer to the Regional/Module 1 Implementation Guide.			

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

9.2.14.2.2 ***application.code***

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
code		[1..1]		This is the container element that organises the coded value for the application.
	code	[1..1]	Text *e.g., us_application_type_1* Refer to Regional/ Module 1 Implementation Guides	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.			
Business Rules	Refer to Regional/Module 1 Implementation Guide for additional information.			

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

9.2.14.3 *Terminology*

All ICH controlled vocabularies are provided in the genericode and spreadsheet files.[21]

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

9.2.14.4 *Excluded Elements*

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

9.2.15 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 system, it can be referenced by its identifier in future uses of the document.

[21] Final Implementation Terminology is provided on the ICH electronic Common Technical Document - eCTD v4.0 website.

9.2.15.1 *Location in XML*

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

- ***controlActProcess>> subject>> submissionUnit>>componentOf1>>submission>> componentOf>>application>> component >> document***

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

Refer to Table 8: v4.0 XML Message Structure for more information.

9.2.15.2 *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

9.2.15.2.1 *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	The ***root*** attribute of the ***id*** element is a global unique identifier of the ***document.***
Conformance	The ***id@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. Note: If the applicant is managing documents across regions, the document identifier may be used across regions, but the document element and physical file must be submitted to each region or agency. Refer to Regional/Module 1 Implementation Guides for additional information.			

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

9.2.15.2.2 ***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]	Text Sender-specified title *e.g., General Information*	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 for Replace*	The ***updateMode*** attribute that is used if updating the ***document.title*** element.
Conformance	The ***title@value*** attribute is required for all documents.			
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 an existing Document title is being changed – i.e., avoid using ***updateMode*** if the title value is the same. Refer to Section 9.2.17.2 for information about updating ***document.title.***			

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

9.2.15.2.3 ***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	[0..1]	Alpha Numeric *e.g., SHA256*	The ***integrityCheckAlgorithm*** is the algorithm type that was used for the checksum values provided in ***integrityCheck*** element.
	language	[0..1]	Alpha Refer to ISO 639.1 for two-letter language codes and Regional/Module 1 Implementation Guides	The ***language*** attribute indicates the language for the document.

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
	mediaType	[0..1]	Text *Designated for future use* Refer to Regional/Module 1 Implementation Guides	The ***mediaType*** attribute specifies the usage for additional processing of the file where it is regionally requested.
	charset	[0..1]	Text e.g., "jp_utf8" or "jp_shift_jis" Refer to Regional/Module 1 Implementation Guides	The ***charset*** attribute specifies the character encoding used in the document.
	updateMode	[0..1]	Alpha *e.g., R for Replace*	The ***updateMode*** attribute provides the coded value to indicate if the ***text*** element's attributes need to be updated.
text.reference		[0..1]		This is the container element within the ***text*** element for a document.
	value	[1..1]	Text File path of the document *e.g., m3/32-body-data/32s-drug-sub/32s1-gen-info.pdf*	The ***value*** attribute of the ***text.reference*** element provides the location of the document with the relative path and filename of the document.

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
text.integrityCheck		[0..1]	Alpha Numeric *e.g., 618102bf07065bcc1250594201fe448515f0fa61*	The ***integritycheck*** element provides the checksum value of the document.
text.thumbnail		[0..1]		The ***thumbnail*** element allows the sender to describe the document in their system.
	value	[1..1]	Text *e.g., 26145c7a-3dc7-404d-91c1-6e0e5c71f8f6 (UUID) or A1234567 (sender-specified value)* Refer to Regional/Module 1 Implementation Guides	The ***value*** attribute allows the applicant to provide a sender-specified value for the document in their system. Note: this value will not be used by the receiver.
text.description		[0..1]		The ***description*** element allows the sender to describe the document.

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
	value	[1..1]	Text *e.g., SAS code for deriving ADaM from SDTM* Refer to Regional/Module 1 Implementation Guides	The ***value*** attribute allows the applicant to provide a sender-specified value that further describes the contents of a document.

Conformance	All new documents require the following elements/attributes:
	• The ***text*** element
	  ○ The ***text@IntegrityCheckAlgorithm*** attribute
	  ○ The ***reference@value*** attribute
	  ○ The ***text.integrityCheck*** element			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	The ***text*** element should be used when sending a new document. This element may not be necessary for updates to an existing document element. For document title updates, the ***text@integrityCheckAlgorithm*** and ***text.integrityCheck*** are not required. All new document elements should include the text element with the ***text@integrityCheckAlgorithm*** attribute and ***text.integrityCheck*** element. The ***text.reference*** element is not required for document title updates, but is required for all other uses of the document element. The ***text.thumbnail*** element will not be used by the receiving party. The ***value*** attribute is for the sender's use only, and ***text.thumbnail*** is provided at the discretion of the sender. The ***text.description@value*** attribute will be regionally specified (e.g., additional information provided for study data documents). Refer to Regional/Module 1 Implementation Guides. The ***text@language and text@charset*** attributes are optional in most cases. Refer to Section 9.2.17.2.2 for information about updating the ***text*** element**.** Refer to Regional/Module 1 Implementation Guides for additional information and complete list of allowable values. For file reuse, the ***text*** element must indicate the same ***reference@value***, ***text@IntegrityCheckAlgorithm*** and ***text.integrityCheck*** values of the previously submitted ***document*** element. The ***reference@value*** should be the relative path to the document. If reuse is in the same submission unit the relative path would be in its respective module folder. If reuse is across submission units the relative path will need to indicate the sequence number and possibly the application number. Refer to Section 9.2.17.3 for information about updating the ***text.reference*** element**.**			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Excluded Elements and/or Attributes	The following datatype elements and attributes may not be required by eCTD v4.0: • ***text.data*** • ***text.xml*** • ***text.translation*** • ***text@compression*** • ***text@controlInformationExtension*** • ***text@controlInformationRoot*** • ***text@flavorId*** • ***text@nullFlavor*** • ***text@validTimeHigh*** • ***text@validTimeLow*** • ***text@value*** • ***text@xsi:type***			

9.2.15.3 *Terminology*

All ICH controlled vocabularies are provided in the genericode and spreadsheet files. [22]

9.2.15.4 *Excluded Elements*

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

9.2.15.5 *XML SAMPLES: Document*

The following XML Samples build the ***document*** element as specified for an Application, including the optional elements and attributes.

```
<document>
    <id root="973d9293-77b9-4f45-b62e-aae62d7ce814"/>
    <title value="Process and Controls"/>
    <text integrityCheckAlgorithm="SHA256" language="jp" charset="jp_utf8">
        <reference value="m3/32-prod/manuf-process-and-controls.pdf"/>
        <thumbnail value="identifier for document from sender's document management system"/>
        <description value="Additional description of the document contents"/>
        <integrityCheck>c0d5623550c997a70b62717d95fca1cada201754d1ed9fbbbbfa97bfd64c8ea4</i
ntegrityCheck>
    </text>
</document>
```

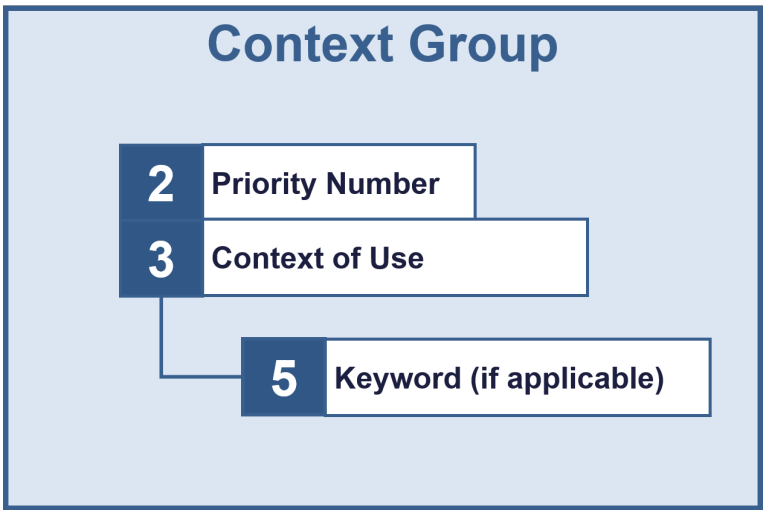
Refer to XML Color Legend for color usage.

[22] Final Implementation Terminology is provided on the ICH electronic Common Technical Document - eCTD v4.0 website.

9.2.16 Approaches to Changes in Context Groups

This section describes the management of ***contextOfUse*** elements that change over time that are part of a context group as defined as more than one Context of Use with the same Context of Use code and Keyword code(s) (when keywords are present). The following figure depicts how the elements are grouped in the same context.

Figure 4: Context Group Model



The following section provides information about using keywords to group one or more Context of Use elements together as well as changes in content composition – i.e., a group of documents may change from one Context of Use to many Context of Use elements, and many to one.

9.2.16.1 *Use of Keywords for Group Title*

The sender may use a keyword to add a group title to the Context of Use to further organise content under a table of contents heading. If the sender knows the CTD heading needs to be organised with a group title, the keyword should be used even if there is only one ***contextOfUse*** element. Only one group title keyword should be applied to the Context of Use.

```
<component>
    <priorityNumber value="1000"/>
    <contextOfUse>
        <id root="1f271446-8d56-4ddc-b730-eaee208c7053"/>
        <code code="ich_3.2.p.7" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <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 Container Keyword Definition "PVDC Blister 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 "Analytical
Procedures" and is an optional keyword type.-->
                <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="2.16.840.1.113883.3.989.2.2.1.1.1"/>
                <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 Container Keyword Definition "PVDC Blister 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 "Analytical
Procedures" and is an optional keyword type.-->
                <referencedBy typeCode="REFR">
                    <keyword>
                        <code code="GT001" codeSystem="2.16.840.1.113883.3"/>
                    </keyword>
                </referencedBy>
            </contextOfUse>
        </component>
```

All Context of Use keywords are shown for illustration purposes only. Refer to the controlled vocabulary and ICH M4 Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use files for the allowable combinations.

Refer to XML Color Legend for color usage.

9.2.16.2 *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

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="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <statusCode code="active"/>
        <!--Document Referenced is Analytical Procedure 1-->
        <derivedFrom>
            <documentReference>
                <id root="164af1e4-f625-4621-8d69-ca56b8f7dc7b"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

Sequence 2

The following sample depicts the replacement of the previous Context of Use with two new Context of Use elements each referencing a document (i.e., the content may be split into two new documents, one document may be revised and one added or both containing new content). The Related Context of Use is a reference back to the identifier of the previous Context of Use, which will reflect one document is replaced by two under the same heading. Note: The priority number is reassigned to the first of the two replacement Context of Use elements. The sender may have assigned a new priority number as well.

```
<component>
    <priorityNumber value="1000"/>
    <contextOfUse>
        <id root="0c0abab8-cbfa-4d2f-9793-2b30ea51b8f5"/>
        <code code="ich_3.2.p.7" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <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>
    </contextOfUse>
</component>
<component>
```

```
        <priorityNumber value="2000"/>
        <contextOfUse>
            <id root="4a5c97e1-4448-47e2-90ff-2d6a264167c0"/>
            <code code="ich_3.2.p.7" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
            <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>
        </contextOfUse>
    </component>
```

Refer to XML Color Legend for color usage.

9.2.16.3 *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="2.16.840.1.113883.3.989.2.2.1.1.1"/>
            <statusCode code="active"/>
            <!--Document Referenced is Analytical Procedure 1-->
            <derivedFrom>
                <documentReference>
                    <id root="164af1e4-f625-4621-8d69-ca56b8f7dc7b"/>
                </documentReference>
            </derivedFrom>
        </contextOfUse>
    </component>
    <component>
        <priorityNumber value="2000"/>
        <contextOfUse>
```

```
            <id root="4a5c97e1-4448-47e2-90ff-2d6a264167c0"/>
            <code code="ich_3.2.p.7" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
            <statusCode code="active"/>
            <!--Document Referenced is Analytical Procedure 2-->
            <derivedFrom>
                <documentReference>
                    <id root="0127b8b6-5510-45c5-93fd-9a3a6e9735aa"/>
                </documentReference>
            </derivedFrom>
        </contextOfUse>
    </component>
```

Sequence 2 – One Document Referenced

The following sample shows that the two previous Context of Use elements are replaced by one Context of Use referencing a document (the document now contains the content previously submitted in two separate documents). Note: The priority number is reassigned to the new ***contextOfUse*** element. The sender may have assigned a new priority number as well.

```
    <component>
        <priorityNumber value="1000"/>
        <contextOfUse>
            <id root="49e18e35-fe1b-4929-bf30-ea58c81ec30f"/>
            <code code="ich_3.2.p.7" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
            <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>
        </contextOfUse>
    </component>
```

Refer to XML Color Legend for color usage.

9.2.16.4 *Changing Granularity*

There may need to be a change to the granularity of CTD headings either based on a change in submission contents or because the heading is no longer valid in the current eCTD implementation. The usage of CTD headings in the current eCTD implementation is specified in the ICH document, Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use. For future changes to submission contents, there may be an effect on the context of use codes or keywords allowed for the respective CTD headings. The following guidance is provided when dealing with changes in granularity.

9.2.16.4.1 *Removal of CTD headings previously allowed*

When a CTD heading is no longer allowed (previously being allowed), the following scenarios may occur:

- Submission contents may continue to be relevant under the existing heading, but additional information may need to be provided.
    - New submission content should be submitted with the new valid context of use codes and keywords.
    - Submission contents will appear under their respective CTD headings and keywords.
    - There will be no relationship (i.e., life cycle) between the existing and new submission contents.
- Submission contents may no longer be relevant, but new submission contents need to be submitted.
    - The existing submission content needs to be suspended (Refer to Section 9.2.11.3.3).
    - New submission content should be submitted with the new valid context of use codes and keywords.
    - Suspended submission content is no longer active, and new submission content will be active under the new CTD headings and keywords.
    - There will be no relationship (i.e., life cycle) between the existing and new submission contents.
- Submission contents need to be replaced, but the CTD headings and/or keywords first need to change.
    - The existing submission content needs to be suspended (Refer to Section 9.2.11.3.3).
    - A new Context of Use is submitted with the new CTD headings, keywords and a reference to the document identifier of the existing submission content.
    - In a future sequence, provide the new submission content under a new Context of Use with the same CTD headings, keywords and a reference to the existing content (i.e., related Context of Use.
    - The submission content will show a relationship between the existing submission content and the new submission content under the new CTD heading and keywords.

9.2.16.4.2 *Adding CTD Headings not previously allowed*

When a CTD heading is now allowed (previously not being allowed) and the submission content at a higher or lower level is better suited under the new CTD heading.

- Submission contents may continue to be relevant under the existing CTD heading, but additional information may need to be provided under the new CTD heading.
    - New submission content should be submitted with the new valid context of use codes and keywords.
    - Submission contents will appear under their respective CTD headings and keywords.
    - There will be no relationship (i.e., life cycle) between the existing and new submission contents.
- Submission contents may no longer be relevant, but new submission contents need to be submitted.
    - The existing submission content needs to be suspended (Refer to Section 9.2.11.3.3).
    - New submission content should be submitted with the new valid context of use codes and keywords.
    - Suspended submission content is no longer active, and new submission content will be active under the new CTD headings and keywords.
    - There will be no relationship (i.e., life cycle) between the existing and new submission contents.
- Submission contents need to be replaced, but the CTD headings and/or keywords first need to change.
    - The existing submission content needs to be suspended (Refer to Section 9.2.11.3.3).
    - A new Context of Use is submitted with the new CTD headings, keywords and a reference to the document identifier of the existing submission content.
    - In a future sequence, provide the new submission content under a new Context of Use with the same CTD headings, keywords and a reference to the existing content (i.e., related Context of Use.
    - The submission content will show a relationship between the existing submission content and the new submission content under the new CTD heading and keywords.

9.2.17 Considerations for the Document Element

9.2.17.1 *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. In addition, all the contents of the reused document, including references and hypertext links to other documents, should be relevant to the submission that reuses the document. Reference to the document

not relevant to the submission should not be submitted by document reuse. The most common examples of document reuse are 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 ***contextOfUse*** element.

Below, the XML shows two ***contextOfUse*** 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.s.2.3" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <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</i
    ntegrityCheck>
    </text>
</document>
```

document.id

Sequence 2

Context of Use Element

```
<component>
    <priorityNumber value="2000"/>
    <contextOfUse>
        <id root="47939431-1ac1-4e17-b44d-dcea7ce43050"/>
```

```
        <code code="ich_3.2.s.2.3" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <statusCode code="active"/>
        <derivedFrom>
            <documentReference>
                <id root="3d1084fb-56c6-4923-a1e5-8a15e4fdc9c5"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

document.id provided in Sequence 1

Refer to XML Color Legend for color usage.

Document Element

The ***document*** element is not sent in this submission unit. The document was sent in the previous sequence 1. In the example above, the document may be a reference from within the same application or across applications. Refer to Regional/Module 1 Implementation Guides for additional information about document reuse.

Document Reuse using Forward Compatibility

In the case of Forward Compatibility, the Document Reference identifier provides the Leaf Reference of the previous v3.2.2 content. The following examples depict the variations that may exist for referencing document within and across applications.

When referencing an existing v3.2.2 document within the same application, it may be used for the application as depicted below in the ***document.id@extension*** value.

```
<component>
    <priorityNumber value="1000"/>
    <contextOfUse>
        <id root="521b3169-4a3e-4e4a-adc9-a36812205fb9"/>
        <code code="ich_3.2.p.1" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.3"/>
        <statusCode code="active"/>
        <derivedFrom>
            <documentReference>
                <id root="2.16.840.1.113883.3.989.2.2.1.13.1"
                extension="0000.ich#NLAS57D17EB601C9EDCA"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

When referencing a document in another application with an application type and number identifier, it may be used for the application as depicted below in the ***document.id@extension*** value.

```
<component>
    <priorityNumber value="1000"/>
```

```
    <contextOfUse>
        <id root="589b8280-19f5-4997-a42d-e7ba8e9d7b74"/>
        <code code="ich_3.2.p.1" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.3"/>
        <statusCode code="active"/>
        <derivedFrom>
            <documentReference>
                <id root="2.16.840.1.113883.3.989.2.2.1.13.1"
                extension="nda123456.0000.ich#NLAS57D17EB601C9EDCA"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

When referencing a document in another application with a unique identifier, it may be used for the application as depicted below in the ***document.id@extension*** value.

```
<component>
    <priorityNumber value="1000"/>
    <contextOfUse>
        <id root="612fa349-d70d-4184-99c1-3f7348e585e6"/>
        <code code="ich_3.2.p.1" codeSystem="2.16.840.1.113883.3.989.2.2.1.1.3"/>
        <statusCode code="active"/>
        <derivedFrom>
            <documentReference>
                <id root="2.16.840.1.113883.3.989.2.2.1.13.1" extension="5f0e8436-e1df-4031-90d3-
                413deff109e5.0000.ich#NLAS57D17EB601C9EDCA"/>
            </documentReference>
        </derivedFrom>
    </contextOfUse>
</component>
```

Refer to Regional/Module 1 Implementation Guide for assignment of application number and appropriate ***id@extension*** value as an OID or UUID.

9.2.17.2 *Document Element Updates*

The ***document*** element includes several attributes that may need to be updated after the initial submission of the element. Changes need to be made based on the initial submission, which includes required and optional elements. Below is an example of the document element with the required and optional elements and attributes.

Initial submission of document

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

```
        <reference value="m3/32-prod/manuf-process-and-controls.pdf"/>
        <integrityCheck>a4c828974a7d177137d69aedfc45379a694611ef317c6c1741a935aa9555c57d</
    integrityCheck>
    </text>
</document>
```

Changes to the document element are summarised in the following subsections for document title update, text element update and update of both document elements. The following condition applies to the updates of both text and title updates:

- If the ***text@integrityCheckAlgorithm, text.integrityCheck*** and ***reference@value*** are submitted with the title and/or text update, the values will be ignored by the receiver. The values for these elements or attributes should remain constant after the initial document is submitted

9.2.17.2.1 *Document Title Updates*

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

Update to Document Title using *updateMode*

The document ***id@root*** value remains the same when fixing an error (e.g., typo) in the ***document.title@value*** attribute. The document title will be updated for all references of the document.

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

If the ***document.title@value*** is completely different (i.e., it is intended to provide a new title) then a new document object should be submitted – i.e., file reuse (see the next section).

9.2.17.2.2 *Document Text Updates*

The ***language*** attribute may be updated, and share the same ***updateMode*** attribute with other text attributes.

The document ***id@root*** value remains the same when fixing an error or missing value in the ***document.text@language*** attribute. The example provided in this section, will indicate the required elements for such an update.

```
<component>
    <document>
        <id root="ceb05f3d-ebb0-4547-9734-056efa134a7a"/>
        <text language="en" updateMode="R"/>
    </document>
</component>
```

Any changes to the document text element – either adding or replacing a value, the ***updateMode*** will provide the value "R" to indicate that the sender intended to overwrite the information previously submitted.

Refer to Regional/Module 1 Implementation Guides for instructions when the ***language*** element should be used.

9.2.17.2.3 *Document Title and Text Updates*

If both the document ***title*** and ***text*** elements need to be updated, instructions are a combination of the individual updates.

The document ***id@root*** value remains the same when fixing an error or missing value in the ***document.title@value,*** or ***document.text@language*** attribute. The example provided in this section, will indicate the required elements for such an update.

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

Refer to XML Color Legend for color usage.

9.2.17.3 *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 (i.e., to use a different document title). In these 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 (Refer to Section 9.2.17.1).

Files can be reused across submissions and applications (see notes 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. The following are possible reuse scenarios:

- Reusing a file that has different 1st level folder (in another application) should include this first level folder name in the path.

A file path example for a file in a different application:

```
<reference value="../../NDA123456/99/m1/promotional_website.pdf"/>
```

- Reusing a file that has different 2nd level folder (in another sequence of the current application) should include the second level folder name in the path

A file path example for a file in the same application:

```
<reference value="../99/m1/promotional_website.pdf"/>
```

- Reusing a file that has the same 2nd level folder (in submission unit content)

A file path example for a file in the same application:

```
<reference value="m1/promotional_website.pdf"/>
```

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 as the originating submission unit.

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".

```
<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>5b94eb14cd31031a4d4539d0bcfbef028a91c04d2d2575990c4422947a9f43
            7a</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="../sequencefolder/m5/531-biopharm/report1.pdf"/>
            <integrityCheck>
5b94eb14cd31031a4d4539d0bcfbef028a91c04d2d2575990c4422947a9f437a </integrityCheck>
        </text>
    </document>
</component>
```

Refer to XML Color Legend for color usage.

9.2.18 Keyword Definition

The ***keywordDefinition*** is used to provide a sender-defined 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 (i.e., sender-defined keywords). A keyword definition contains name value pairs that are used to provide Keywords on the Context of Use. Note: Keyword Definitions may be defined by the applicant in a manner which they may be reused across applications (even though they must be submitted for each application).

9.2.18.1 *Location in XML*

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

- ***controlActProcess>> subject>> submissionUnit>>componentOf1>>submission>> componentOf>>application>> referencedBy> >keywordDefinition***

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

Refer to Table 8: v4.0 XML Message Structure for more information.

9.2.18.2 *XML Elements provide*

The following tables 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-defined 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.

9.2.18.2.1 ***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.

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
	code	[1..1]	Text *e.g., ich_keyword_type_1 i.e., ICH or Regional code type* Refer to Regional/Module 1 Implementation Guide	The ***code*** attribute for the coded value of the type of keyword definition.
	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	The ***code*** and ***codeSystem*** are required attributes.			
Business Rules	The ***code*** must be from a valid ICH Keyword code type.			
Excluded Elements and/or Attributes	The following datatype elements and attributes may not be required by eCTD v4.0: • ***code.displayName*** • ***code.originalText*** • ***code.translation*** • ***code.source*** • ***code@codeSystemName*** • ***code@codeSystemVersion*** • ***code@codingRationale*** • ***code@controlInformationExtension*** • ***code@controlInformationRoot*** • ***code@flavorId*** • ***code@id*** • ***code@nullFlavor*** • ***code@updateMode*** • ***code@validTimeLow*** • ***code@validTimeHigh*** • ***code@valueSet*** • ***code@valueSetVersion*** • ***code@xsi:type***			

9.2.18.2.2 *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*	The ***code*** attribute provides the value for the status.
Conformance	The ***statusCode*** is required.			
Business Rules	The ***code*** attribute should always have a value of "active".			
Excluded Elements and/or Attributes	The following datatype elements and attributes may not be required by eCTD v4.0: • ***statusCode@controlInformationExtension*** • ***statusCode@controlInformationRoot*** • ***statusCode@flavorId*** • ***statusCode@nullFlavor*** • ***statusCode@updateMode*** • ***statusCode@validTimeHigh*** • ***statusCode@validTimeLow*** • ***statusCode@xsi:type***			

9.2.18.2.3 *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]	Text Sender-defined value *e.g., MANU001 or MFR_001*	The ***code*** attribute for the keyword being defined.

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
	codeSystem	[1..1]	Text Sender-defined value	The ***codeSystem*** value that is a unique identifier for the controlled vocabulary system.
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]	Text Sender-defined value *e.g., Big Manufacturer*	The ***displayName*** attribute of the ***value*** element of the keyword being defined.
	updateMode	[0..1]	Alpha *e.g., R for 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. If there is a conflict with ***the keywordDefinition.value.item@code*** and ***keywordDefinition.value.displayName*** – i.e., an update is not being made with ***updateMode*** and a new ***displayName@value*** is provided for an existing code, the submission unit will be rejected.			

Element	Attribute	Cardinality	Value(s) Allowed *Examples*	Description *Instructions*
Business Rules	Each ***keywordDefinition*** can only contain one sender-defined 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. For forward compatibility, each ***value.item@code*** and ***value.item.displayName@value*** combination must match an existing v3.2.2 attribute type and value to ensure v4.0 and v3.2.2 content is grouped together for display and life cycle. No changes to the value should be made – i.e., abbreviations or reformatting may cause errors in the transition. See Section 9.2.18.5.1 for additional instructions for the values assigned to the Study Id Study Title keyword type.				
Excluded Elements and/or Attributes	The following datatype 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***			

9.2.18.3 *Terminology*

All ICH controlled vocabularies are provided in the genericode and spreadsheet files.[23]

9.2.18.4 *Excluded Elements*

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

9.2.18.5 *Guidance regarding Keyword Definition values*

This section outlines any special instructions for specific keyword definition types (i.e., sender-defined concepts). These guidelines should be followed to ensure correct usage of the information by each region (Refer to Regional/Module 1 Implementation Guides for additional validation rules).

[23] Final Implementation Terminology is provided on the ICH electronic Common Technical Document - eCTD v4.0 website.

9.2.18.5.1 *Study Id Study Title*

When submitting the value for the Study Id Study Title keyword type the two values should be concatenated with an underscore dollar sign (_$) as follows: studyID_$studyTitle.

An example of the keyword definition value would appear as follows:

```
<referencedBy>
        <keywordDefinition>
            <code code="ich_keyword_type_8"
            codeSystem="2.16.840.1.113883.3.989.2.2.1.5.2"/>
            <statusCode code="active"/>
            <value>
               <item code="STDYID_TITLE001" codeSystem="2.16.840.1.113883.3">
                  <displayName value="Study0001_$StudyABC"/>
               </item>
            </value>
     </keywordDefinition>
 </referencedBy>
```

9.2.18.6 *XML SAMPLES: Keyword Definition*

At this time, keywords should only be defined for an application. However, the same keyword definitions (code and value pair) may be resubmitted across applications to allow for specific regional business scenarios (e.g., grouped submissions). The following sections outline the additional scenarios for XML instances in defining and using keywords.

9.2.18.6.1 *Keyword Definitions*

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

```
<referencedBy>
        <keywordDefinition>
            <code code="ich_keyword_type_3"
            codeSystem="2.16.840.1.113883.3.989.2.2.1.5.2"/>
            <statusCode code="active"/>
            <value>
               <item code="MANU001" codeSystem="2.16.840.1.113883.3">
                  <displayName value="Big Manufacturer"/>
               </item>
            </value>
     </keywordDefinition>
 </referencedBy>
```

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

Refer to XML Color Legend for color usage.

9.2.18.6.2 *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>
        <code code="ich_keyword_type_3" codeSystem="2.16.840.1.113883.3.989.2.2.1.5.2"/>
        <statusCode code="active"/>
        <value>
            <item code="MANU001" codeSystem="2.16.840.1.113883.3">
                <displayName value="Ace Manufacturer"/>
            </item>
        </value>
    </keywordDefinition>
</referencedBy>
```

Sequence 2

```
<referencedBy>
    <keywordDefinition>
        <code code="ich_keyword_type_3" codeSystem="2.16.840.1.113883.3.989.2.2.1.5.2"/>
        <statusCode code="active"/>
        <value>
            <item code="MANU001" codeSystem="2.16.840.1.113883.3">
                <displayName value="Acme Manufacturer" updateMode="R"/>
            </item>
        </value>
    </keywordDefinition>
</referencedBy>
```

displayName changed to correct value.

Note: The Display Name update is intended to apply the changes to all Submission Units (including those submitted in the past) within the same Application. The update will not apply to submission units on file for other Applications. If the display name update is expected to apply to a specific Submission Unit, a new Keyword Definition should be defined.

9.2.18.7 *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_keyword_type_3"
        codeSystem="2.16.840.1.113883.3.989.2.2.1.5.2"/>
        <statusCode code="active"/>
        <value>
            <item code="MANU003" codeSystem="2.16.840.1.113883.3">
                <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="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <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="2.16.840.1.113883.3"/>
            </keyword>
        </referencedBy>
        <referencedBy typeCode="REFR">
            <keyword>
                <code code="SUB001" codeSystem="2.16.840.1.113883.3"/>
            </keyword>
        </referencedBy>
    </contextOfUse>
</component>
```

All Context of Use keywords are shown for illustration purposes only. Refer to the controlled vocabulary and ICH M4 Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use files for the allowable combinations.

Refer to XML Color Legend for color usage.

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="2.16.840.1.113883.3.989.2.2.1.1.1"/>
        <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="2.16.840.1.113883.3"/>
            </keyword>
        </referencedBy>
        <referencedBy typeCode="REFR">
            <keyword>
                <code code="SUB001" codeSystem="2.16.840.1.113883.3"/>
            </keyword>
        </referencedBy>
    </contextOfUse>
</component>
```

All Context of Use keywords are shown for illustration purposes only. Refer to the controlled vocabulary and ICH M4 Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use files for the allowable combinations.

Refer to XML Color Legend for color usage.

9.2.19 XML SAMPLE: Study-Id and Title

The following XML sample shows one ***keywordDefinition*** of type, Study-Id and Title. The Study Id value should be separated from the title with underscore dollar sign set of characters (_$). As an example, existing values in the STF are "Study-001" and "Title A", and would be converted to "Study-001_$Title A". It is very important to include the underscore dollar sign (_$) between the two keywords so that the validation rules will not reject the lifecycle of content, especially with forward compatibility.

```
<referencedBy>
        <keywordDefinition>
            <code code="ich_keyword_type_8"
            codeSystem="2.16.840.1.113883.3.989.2.2.1.95.2"/>
            <statusCode code="active"/>
            <value>
               <item code=" STDY1-TITLE1" codeSystem="2.16.840.1.113883.3">
                  <displayName value="Study-001_$Title A"/>
               </item>
            </value>
    </keywordDefinition>
 </referencedBy>
```

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

Refer to XML Color Legend for color usage.

10. 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.

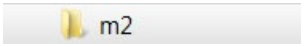
11. APPENDIX 1:SAMPLE FILES AND FOLDERS FOR MODULES 2 – 5

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 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

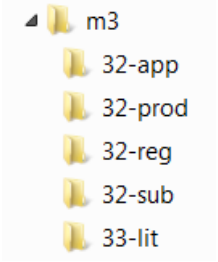


11.2 Module 3 Quality

The name of the folder for module 3 should be m3. The folders in module 3 should be named as presented in the table below, but can be changed to further reduce or omit folders to minimise path length issues. Additional folders should only be provided to organise files with the same name.

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

Figure 6: Module 3 Folder Structure

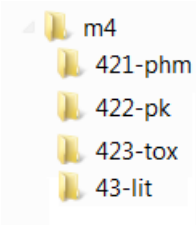


Section in CTD	Description	Folder Name
3.2.A	Appendices	*32-app*
3.2.P	Drug Product	*32-prod*
3.2.R	Regional Information	*32-reg*
3.2.S	Drug Substance	*32-sub*
3.3	Literature References	*33-lit*

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 presented in the table below, but can be changed to further reduce or omit folders to minimise path length issues. The m4 folder structure is depicted in Figure 7: Module 4 Folder Structure.

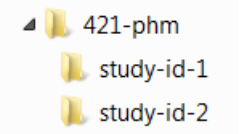
Figure 7: Module 4 Folder Structure



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 organise 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) as depicted in Figure 8: Example of Study folders. Refer to Regional/Module 1 Implementation Guides for rules additional folders in this module.

Figure 8: Example of Study folders



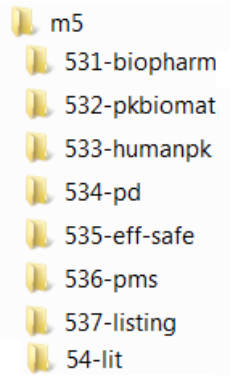
11.4 Module 5 Clinical Study Reports

The name of the folder for module 5 should be m5. The folders in module 5 should be named as presented in the table below, but can be changed to further reduce or omit folders to minimise path length issues.

- The CTD organisation provides locations for case report forms and individual patient data listings in Module 5.3.7. Refer to 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.

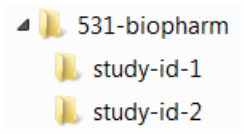
Figure 9: Module 5 Folder Structure



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	*537-listing*
5.4	Literature References	*54-lit*

Additional folders may be added to organise 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) as depicted in Figure 10: Example of Study Folders. 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

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 9.2.

- 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
	Controlled Vocabulary	Code value is active
	Submission Unit	Submission Unit identifier is required (1..1)
		Submission Unit id root must be a UUID
		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"
		The Submission Unit must have at least one Context of Use element in the message
	Sequence Number	Sequence Number is required (1..1)
		Sequence Number must be a whole number between 1 and 999999
		Sequence Number for initial submission unit in the application starts with "1"

Category	Type/Element	Validation Criteria
		Sequence Number is unique in the application for the applicant
		The Sequence Number must have one and only one value for the Submission element
	Context of Use Priority Number	Context of Use Priority Number is required
		Context of Use Priority Number must be a non-negative real number
		Context of Use Priority Number shall have one and only one value
	Context of Use	Context of Use identifier is required
		Context of Use id root must be a unique identifier
		Context of Use code must be valid for the referenced code system
		Context of Use status code element is required
		Context of Use status code value can only be "active" or "suspended"
		A Context of Use identifier or v3.2.2 Leaf Reference must already exist when using the status code of “suspended
		Context of Use code system is a valid OID
	Related Context of Use	Related Context Of Use identifier is required when Related Context Of Use is provided
		Context of Use and Related Context of Use referenced must have the same Context of Use code and Keyword code combination (or matching v3.2.2 equivalents)
		Related Context of Use id root can only reference previously submitted active Context of Use identifiers or v3.2.2 Leaf Reference
	Document Reference	Document Reference identifier is required for all active new Context of Use elements
		Document Reference element not allowed for suspended Context of Use elements
		Document referenced in the CoU must exist
	Keyword	Keyword code is required for each keyword element on a Context of Use
		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
		Required keywords for a Context of Use code attribute must be included
		The Keyword Type must be valid for the Context of Use heading
		On each Context of Use element, a valid Keyword Type shall only be used once
		Submission identifier is required (1..1)

Category	Type/Element	Validation Criteria
	Submission	Submission identifier is a UUID
		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 identifier must have a valid value
		Document id root must be a UUID
		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)
		Document path is required
		Document path must exist
		Document identifier must be referenced by a CoU
	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
		Keyword definition display name value is as previously submitted
		The Keyword Definition for a Study Id and Study Title (ich_keyword_type_8) must follow the correct format
		Keyword definition must exist and match v3.2.2 value
		Keyword Definition code system is a valid OID
Submission Package	Submission Package	Submission Unit file is named submissionunit.xml exists
		Checksum file named sha256.txt exists
		Only one Submission Unit file is allowed
		Submission Unit checksum file value is valid

Category	Type/Element	Validation Criteria
		Submission Unit File is found in the sequence number folder
		Document checksum value is valid
		File name length is met
		Folder name length is met
		Folder path length is met
		The folder path value only contains the allowable special characters
		Unassociated file found

12.2 Message Validation Rules

The processing of a submission unit that fails to meet one or more of these criteria will be returned to the applicant for correction and resubmission. The sender may use the same sequence number for resubmission

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 the schema validations
Controlled Vocabulary Versioning				
eCTD 4-079	Business Rule	Code value is active	The code value is retired	The submission unit needs to be resubmitted with active code values.
Submission Units				
eCTD 4-003	Schema	Submission Unit identifier is required (1..1)	The ***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 UUID	The ***submissionUnit.id@root*** is not a UUID	The submission unit needs to be resubmitted with the Submission Unit UUID
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

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
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
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
eCTD 4-011	Business Rule	The Submission Unit must have at least one Context of Use element in the message	The submission unit does not have any Context of Use elements	The submission unit needs to be resubmitted with at least one Context of Use element
Sequence Number				
eCTD 4-012	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 4-013	Business Rule	Sequence Number must be a whole number between 1 and 999999	The sequence number value is not a whole number between 1 and 999999	The submission unit may need to be resubmitted with a sequence number value between 1 and 999999
eCTD 4-014	Business Rule	Sequence Number for initial submission unit in the application starts with "1"	The sequence number for the initial submission unit in an application is not the value "1"	The submission unit needs to be resubmitted with the sequence number value of 1

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-015	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 4-016	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 4-017	Schema	Context of Use Priority Number is required	The priority number value is not provided	The submission unit needs to be resubmitted providing priority numbers
eCTD 4-018	Business Rule	Context of Use Priority Number must be a whole number between 1 and 999999	The priority number value is not a whole number between 1 and 999999	The submission unit needs to be resubmitted with a priority number value between 1 and 999999
eCTD 4-019	Schema	Context of Use Priority Number shall have one and only one value	There is more than one Context of Use priority number provided for each Context of Use	The submission unit needs to be resubmitted providing priority numbers
Context of Use				
eCTD 4-020	Schema	Context of Use identifier is required	The ***contextOfUse.id@root*** is not provided	The submission unit needs to be resubmitted providing a Context of Use identifier
eCTD 4-021	Schema	Context of Use id root must be a unique identifier	The ***contextOfUse.id@root*** value is not a UUID or combination of namespace OID and local value for the namespace	The submission unit needs to be resubmitted with a Context of Use unique identifier

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-075	Business Rule	Context of Use code must be valid for the referenced code system	Context of Use code is not a valid value for the referenced code system	The submission unit needs to be resubmitted providing a value for the Context of Use code for the referenced code system
eCTD 4-022	Schema	Context of Use status code element is required	The ***contextofUse.statusCode*** element is not provided	The submission unit needs to be resubmitted with a status code for each Context of Use
eCTD 4-023	Schema	Context of Use status code value can only be "active" or "suspended"	The ***contextOfUse.statusCode@code*** value is not "active" or "suspended"	The submission unit needs to be resubmitted with a valid status code for the Context of Use
eCTD 4-080	Business Rule	A Context of Use identifier or v3.2.2 Leaf Reference must already exist when using the status code of “suspended”	The Context of Use identifier or v3.2.2 Leaf Reference is not found in a previous submission unit	The submission unit needs to be resubmitted providing an existing value for the Context of Use identifier or v3.2.2 Leaf Reference
eCTD 4-081	Business Rule	Context of Use code system is a valid OID	The ***contextOfUse.code@codeSystem*** is not a valid registered or known OID	The submission unit needs to be resubmitted with a valid context of use code system
Related Context of Use				
eCTD 4-024	Schema	Related Context Of Use identifier is required when Related Context Of Use is provided	The ***relatedContextOfUse.id@root*** attribute is not provided	The submission unit needs to be resubmitted providing a Related Context Of Use identifier

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-025	Business Rule	Context of Use and Related Context of Use referenced must have the same Context of Use code and Keyword code combination (or matching v3.2.2 equivalents)	The ***contextOfUse.code@code*** and ***keyword.code@code*** combination (or matching v3.2.2 equivalents) does not match the previous Context of Use referenced in the related Context of Use	The submission unit needs to be resubmitted with corrections to resolve the inaccurate use of related Context of Use
eCTD 4-026	Business Rule	Related Context of Use id root can only reference previously submitted active Context of Use identifiers or v3.2.2 Leaf Reference	The ***relatedContextOfUse.id@root*** does not reference a previously submitted active Context of Use identifier or Leaf Reference; or an identifier or Leaf Reference does not exist or is not allowed by the Region	The submission unit needs to be resubmitted referencing a previously submitted active Context of Use or Leaf Reference
Document Reference				
eCTD 4-027	Business Rule	Document Reference identifier is required for all active new Context of Use elements	The ***documentReference.id@root*** attribute is not provided when the new Context of Use is active	The submission unit needs to be resubmitted with a Document Reference identifier when the new Context of Use is active
eCTD 4-028	Schema	Document Reference element not allowed for suspended Context of Use elements	The ***documentReference*** element is provided when the Context of Use is suspended	The submission unit needs to be resubmitted without a Document Reference when the Context of Use is suspended
eCTD 4-076	Business Rule	Document referenced in the CoU must exist	The document referenced in the CoU cannot be found	The submission unit needs to be resubmitted with an existing v4.0 document identifier or v3.2.2 Leaf Reference
Keyword				

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-029	Schema	Keyword code is required for each keyword element on a Context of Use	The ***keyword.code@code*** attribute is not provided	The submission unit needs to be resubmitted providing a Keyword code for each ***keyword*** element on a Context of Use
eCTD 4-030	Schema	Keyword code system is required for each keyword element	The ***keyword.code@code System*** is not provided	The submission unit needs to be resubmitted providing a Keyword code system for each Keyword code
eCTD 4-031	Business Rule	Keyword code system must be a valid OID	The ***keyword.code@code System*** is not a valid registered or known OID	The submission unit needs to be resubmitted with a valid keyword code system
eCTD 4-032	Business Rule	Keyword code system must have a valid value	The ***keyword.code@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
eCTD 4-070	Business Rule	Required keywords for a Context of Use code attribute must be included	A required ***keyword.code@code*** is not submitted for the Context of Use heading	The submission unit needs to be resubmitted with all required keywords for the Context of Use
eCTD 4-071	Business Rule	The Keyword Type must be valid for the Context of Use heading	The Keyword code value(s) ***contextOfUse.code*** submitted for the Context of Use heading is (are) invalid for the eCTD heading	The submission unit needs to be resubmitted with valid keyword types for the Context of Use
eCTD 4-072	Business Rule	On each Context of Use element, a valid Keyword Type shall only be used once	The same Keyword type has been used more than once for the Context of Use element	The submission unit needs to be resubmitted with only one Keyword of the same Keyword type for each Context of Use
Submission				

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-033	Schema	Submission identifier is required (1..1)	The ***submission.id.item@root*** is not provided	The submission unit needs to be resubmitted with a submission identifier
eCTD 4-077	Business Rule	Submission identifier is a UUID	The ***submission.id.item@root*** is not a UUID	The submission unit needs to be resubmitted with a Submission UUID
eCTD 4-034	Schema	Submission code is required (1..1)	The ***submission.code@code*** attribute is not provided	The submission unit needs to be resubmitted providing a Submission code
eCTD 4-035	Business Rule	Submission code must have a valid value for the region	The ***submission.code@code*** is not a valid value	The submission unit needs to be resubmitted with valid Submission code
eCTD 4-036	Schema	Submission code system is required (1..1)	The ***submission.code@codeSystem*** is not provided	The submission unit needs to be resubmitted providing a Submission code system
eCTD 4-037	Business Rule	Submission code system must have a valid regional code system OID	The ***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 4-038	Schema	Application identifier is required (1..1)	The ***application.id.item@root*** is not provided	The submission unit needs to be resubmitted with an application identifier
eCTD 4-039	Schema	Application code is required	The ***application.code@code*** attribute is not provided	The submission unit needs to be resubmitted providing an Application code
eCTD 4-040	Business Rule	Application code must have a valid value	The ***application.code@code*** is not a valid value	The submission unit needs to be resubmitted with a valid Application code value
eCTD 4-041	Schema	Application code system is required	The ***application.code@codeSystem*** is not provided	The submission unit needs to be resubmitted providing an Application code system

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-042	Business Rule	Application code system is a valid OID	The ***application.code@codeSystem*** is not a valid OID	The submission unit needs to be resubmitted with a valid Application code system
Document				
eCTD 4-043	Schema	Document identifier is required (1..1)	The ***document.id@root*** is not provided	The submission unit needs to be resubmitted providing the Document identifier
eCTD 4-044	Business Rule	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 4-045	Business Rule	Document id root must be a UUID	The ***document.id@root*** value is not a UUID	The submission unit needs to be resubmitted with a Document UUID
eCTD 4-046	Business Rule	Document identifier is unique (i.e., it is not a duplicate identifier and not an update to a document title)	The Document identifier is not unique	The submission unit needs to be resubmitted with a correction to the unique identifier
eCTD 4-047	Business Rule	Document title is required	The ***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 4-048	Business Rule	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)	*The* ***document.text.integrityCheck*** value is not provided for the document element	The submission unit needs to be resubmitted with a checksum value for all documents

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-049	Business Rule	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)	The ***document.text.integrityCheck*** value is not a valid checksum	The submission unit needs to be resubmitted with a valid checksum value for all documents
eCTD 4-050	Business Rule	Document path is required	The ***document.text.reference@value*** is not provided and ***updateMode*** is not present indicating a document title change	The submission unit needs to be resubmitted with a document path for all documents
eCTD 4-051	Business Rule	Document path must exist	The document path provided in the eCTD XML (i.e., ***reference*** element is present) does not physically exist	The submission unit needs to be resubmitted with a correct document path
eCTD 4-082	Business Rule	Document identifier must be referenced by a CoU	A New Document in the submissionUnit.xml is not referenced by a CoU within that submissionUnit.xml	The submission unit needs to be resubmitted with all new document objects referenced by a CoU
Keyword Definition				
eCTD 4-052	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
eCTD 4-053	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 4-054	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

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-055	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 4-056	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 4-057	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 4-058	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***
eCTD 4-068	Business Rule	Keyword definition display name value is as previously submitted	The ***keywordDefinition.value.item.displayName@value*** provided does not match the value previously submitted and ***updateMode*** is not present	The submission unit needs to be resubmitted providing the ***keywordDefinition.value.item.displayName@value*** with update mode to make a change to the keyword definition's display name value
eCTD 4-073	Business Rule	The Keyword Definition for a Study Id and Study Title (ich_keyword_type_8) must follow the correct format	A Keyword Definition with ***keywordDefinition.code@code*** value of ich_keyword_type_8 does not have the ***keywordDefinition.value.item.displayName@value*** formatted as studyID_$studyTitle	The Submission unit needs to be resubmitted providing the correct format for all Keyword Definition for the Study Id and Study Title

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-078	Business Rule	Keyword definition must exist and match v3.2.2 value	The ***displayName*** value of the Keyword Definition element does not exist or match the v3.2.2 value	The submission unit needs to be resubmitted providing the exact v3.2.2 values for the eCTD v4.0 keyword definition display name
eCTD 4-083	Business Rule	Keyword Definition code system is a valid OID	The ***keywordDefinition.code@codeSystem*** is not a valid registered or known OID	The submission unit needs to be resubmitted with a valid keyword definition code code system

12.3 Submission Package Validation Rules

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-059	Business Rule	Submission Unit file is named submissionunit.xml exists	The submission unit file is not found. It may be in another location or may not be named submissionunit.xml or is in mixed case format	The filename should be corrected to the specified naming convention required for eCTD v4.x
eCTD 4-060	Business Rule	Checksum file named sha256.txt exists	The checksum file is not found. It may be in another location or may not be named sha256.txt or is in mixed case format	The submission unit needs to be resubmitted with the sha256.txt file in the correct location and named sha256.txt
eCTD 4-061	Business Rule	Only one Submission Unit file is allowed	There is more than one submissionunit.xml file included in the submission package that is intended for the one validation check	The submission unit needs to be resubmitted with just one submissionunit.xml file
eCTD 4-062	Business Rule	Submission Unit checksum file value is valid	The submission unit checksum in the sha256.txt file does not match the calculated checksum for the submissionunit.xml file	The submission unit needs to be resubmitted with a valid checksum sha256.txt file

No Unique ID	Category	Validation Criteria	Issue Description	Corrective Action
eCTD 4-063	Business Rule	Submission Unit File is found in the sequence number folder	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 4-064	Business Rule	Document checksum value is valid	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 4-065	Business Rule	File name length is met	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 4-066	Business Rule	Folder name length is met	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 4-067	Business Rule	Folder path length is met	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
eCTD 4-074	Business Rule	The folder path value only contains the allowable special characters	The folder path value in the ***text.reference@value*** attribute includes invalid special characters	The submission unit needs to be resubmitted with only allowable special characters in the folder path
eCTD 4-069	Business Rule	Unassociated file found	There is a file found in the submission folder structure that is not referenced as a document or Context of Use	The submission unit needs to be resubmitted with all files associated with a document and Context of Use element