IND CTOC Prototype Demonstration Model Beta 0.4

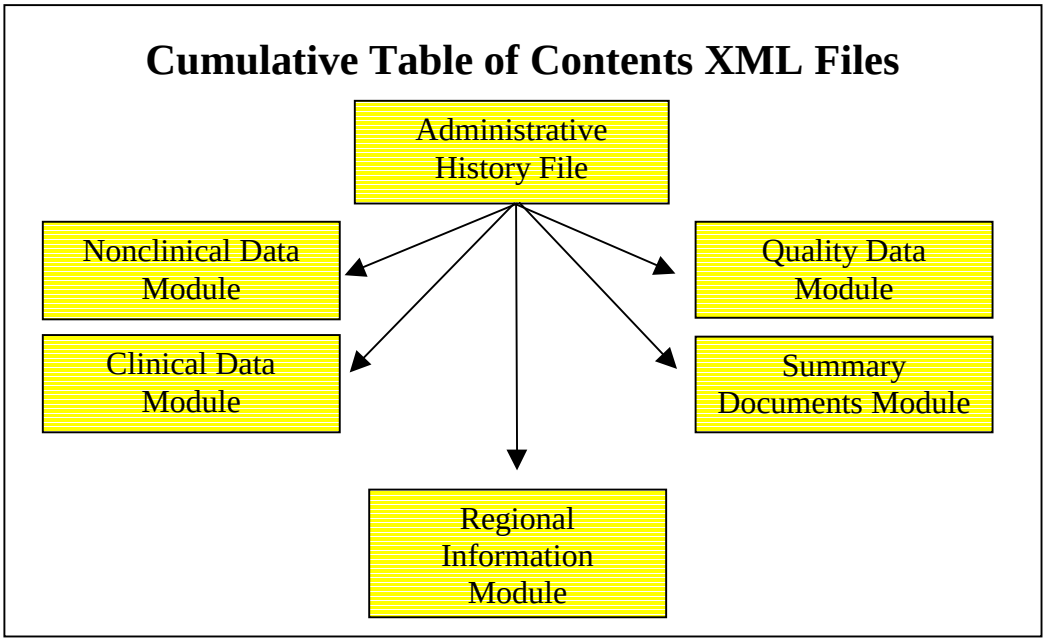
I. BACKGROUND

The FDA is working with the International Conference on Harmonization (ICH) to incorporate XML submission standards in the electronic submission process. As part of this effort, we are evaluating new technology for reviewing electronic applications. We are requesting comments on the use of extensible markup language (XML) in creating a cumulative table of contents (CTOC) for use with IND demonstration applications. This document provides specifications for prototype CTOC XML files for IND demonstration applications. For more information please see the following WWW site: http://www.fda.gov/cder/regulatory/ersr/ctoc/default.htm .

A. Overview of the cumulative table of contents

The cumulative table of contents consists of a series of tagged ASCII files using XML. With each submission, a sponsor would provide a single administration history XML file that includes information about each submission provided up to and including the current submission. In addition, the sponsor would provide an XML file for each module of the application listing all documents and datasets included in each submission up to and including the current submission. The modules are based on the ICH common technical document and include the summary documents, quality data , nonclinical data, clinical data, and regional information. The relationship of these files to the administrative history file is shown in the figure below.

Reviewers would access the XML files using their browser with cascading style sheets (CSS) and Java script developed and supplied by the agency.



B. Overview of XML

XML was developed by a working group at the World Wide Web Consortium (W3C). It is a non proprietary language developed to improve on previous mark up languages including standard generalized markup language (SGML) and hypertext markup language (HTML). XML is not as complicated to use as SGML and is more flexible than HTML.

Information in an XML file is divided into specific pieces. These pieces are called objects or element types. The element type identifies the piece of information. For example, the IND application number might be identified with the element type <appNum>. All element type names are bracketed using the special characters <>. Inside the XML document, the element type name is placed just prior to the piece of information and after the information. This is called tagging. So, in the XML file, the application number for IND 123456 would be tagged as follows <appNum>123456</appNum>. The / prior to the element type denotes that this is the end of the information about the appNum.

By using a hierachial structure, XML allows you to relate two or more elements. This is accomplished by nesting one element within another.

Additional information about the element type is provided by attributes. Attributes are placed within the element types and are surrounded by " ". For example, if you wanted to identify the type of the application number as an IND, you could add this piece of information as an attribute. This could be represented in the XML file as <appNum type="IND">123456</appNum>.

XML files are read by a parser found in internet browsers. Style sheets provide the browser with the information necessary to create tables, fonts, and colors for display.

The specific names of the element types and attributes as well as the valid syntax, structure and format for defining the XML elements are included in a file called document type declaration (DTD). If the XML document does not follow the DTD, then the file may not be able to be used properly.

At the beginning of the XML file, The top three lines of the XML file should include the XML version, the style sheet type and address, and the DTD name and address.

We use XML version 1.0 recommended by the W3C. Additional information can be found at the W3C web site at www.w3c.org.

II. SPECIFICATIONS FOR THE CTOC XML FILES

A. Specifications for the Administration history file

The administrative history XML file contains application identification information, reference to each module's XML table of contents file (module toc), and a record of every submission to the application including the current one. The information in the administration history file would be a complete cumulative history of the application. Each administration history file would be replaced the previously submitted administration history file. A summary of the elements and attributes for the administrative history file is in Table 1

Table 1 Elements and attributes of the administrative history file

<elements> "attributes"	**Comments**
<administration>	Used for organizing purposes
<applicationNum>	Application number
"type"	Type of application being submitted
<productName>	Basic identification -Product Name
<applicant>	Basic identification -Applicant name
<approvalDate>	Basic identification -Approval date or pending
<toc>	Used to link to the module TOC files
"module"	Type of the module toc file
"link"	Name of Module toc file
<history>	Used to organize the submission history files
<submission>	One element for each submission
"type"	Type of submission such as original submission, annual report, supplement, presubmission, correspondence
"serialNumber"	Serial number for the submission type
"date"	Letter date/1571 form date for submission
"submissionCode"	Code for submission date so the exact letter date is not needed for the submission date of files
"clinical"	Identifies what information in included in the submission
"quality"	Identifies what information in included in the submission
"nonclinical"	Identifies what information in included in the submission
"summaries"	Identifies what information in included in the submission
"regional"	Identifies what information in included in the submission

The top three lines of the admin.xml file contain the declaration. The declaration for the admin.xml file is as follows:

```
<?xml version="1.0"?>
<?xml:stylesheet type="text/xsl"
href="http:\\www.fda.gov\cder\XML_Resource\CTOC\administration_v0
02.xsl"?>
```

<!DOCTYPE toc SYSTEM
"http:\\www.fda.gov\cder\XML_Resource\CTOC\administration_v003.dtd
">

The elements and attributes for the admin.xml file are described below.

1. *Element <administration>*

This is the root element used to organize the elements included in the administration history file. All other elements are nested in this element as its child elements. It has no other content. Its end tag (</administration>) marks the end of the administration history file.

2. *Element <applicationNum>*

This is the first element after administration element and only occurs once. It contains the application number. This element has one attribute called type. For example, application 123456 would be represented as:
<appNum>123456</appNum>

a) Attribute <appNum> "type"

The "type" attribute within the <appNum> element provides the type of application to which the submission belongs. IND is the value of the "type" attribute for an investigational new drug application. Building on the previous example, an IND application submission may appear as follows:

<appNum type="IND">123456</appNum>

3. *Element <productName>*

This is the second element and it occurs only once. It contains the name of the drug product. It may be left blank.

4. *Element <applicant>*
This is the third element after the root element and it occurs only once. It contains the sponsor's name.

5. *Element <approvalDate>*
This is the fourth element after the root element and it occurs only once. It contains the date upon which the application was approved. For all IND submissions, it should contain the word "pending".

6. Element <toc>

This is the fifth element after the root element. There is exactly one <toc> element for each module's TOC file. For example, after many electronic submissions to the Quality module of an application, there should still be only one Quality <toc> element.

The <toc> element is empty with four attributes: module, link, submissioncode, and section. Together, the link, submissioncode, and section attributes provide the hypertext link to the module's TOC file.

a) Attribute <toc> "module"

The value of the "module" attribute is the appropriate module of the application, either regional, summaries, quality, nonclinical, or clinical.

b) Attribute <toc> "link"

The value of the "link" attribute is the complete filename of TOC file being listed. The folder and subfolder path is not needed since this is provided by the other <toc> attributes. The TOC file may have any name as long as it is accurately referenced as the value of this attribute.

c) Attribute <toc> "submissionCode"

The "submissionCode" attribute is the key to the submission date. The value of this attribute is a code selected by you and associated with the submission date in the <submission> "date" attribute. The submission element and it's attributes code and date are discussed later. When the value of the "submissionCode" attribute also appears as the value of a <submission> element's "code" attribute it becomes associated with the same <submission> element's "date" attribute.

7. Element <history>

The <history> element appears after the last <toc> element in the administration history file and it appears only once. The <history> element contains all of the administration history file elements described later in this document as child elements. The history element has no other content.

8. Element <submission>

A <submission> element is provided for each electronic submission that has been made to the application. There is no limit to the number of <submission> elements in the administration history file. The <submission> element has no content, but has the following attributes: sameday, type, sequence, date, code, filing, labeling, efficacy, quality, safety, summaries, and regional. These attributes are described below:

a) Attribute <submission> “type”
This “type” attribute value indicates the type of submission that is being provided. It is one of the letters M, Y or I. These letters are associated with submission types in the Table 2.

Table 2 Submission types

M	Presubmission
I	Investigational New Drug (IND)
Y	Annual Report

b) Attribute <submission> “serialNumber”
The “serialNumber” attribute is used to indicate the serial number of the submission and is zero based. For example, the first IND submission has a serialNumber value of 0000 and the second has a value of 0001.

c) Attribute <submission> “date”
This attribute is the letter date for the submission in the form of the ISO 8601 format. The letter date is the date used on the cover letter and submission form (e.g., 1571 form). For example, 14th day of June in the year 2000 has the value of 2000-06-14. This attribute provides the date portion of a link directory path.

d) Attribute <submission > “code”
The value of the “code” attribute is a unique alphanumeric string code of your choice that is associated with the “date” attribute within that <submission> element. For example, the code “amendment 2” can be associated with the date 2000-06-28 in the following way:

```
<submission date=“2000-06-28”
code=“amendment_2”/>
```

Building on this example to include the type and serial number information for an IND it may appear as follows:

```
<submission type=“I” serialNumber= “0002”
date=“2000-06-28”  code=“amendment 2”/>
```

e) Attributes <submission> “filing”
The value of the “filing” attribute indicates the filing mechanism or reporting category used for reporting changes to a previous submission. The value of this attribute is restricted to those listed in the DTD. The allowed values for an IND is AM for amendment.

f) Attributes <submission> “clinical”, “quality”, “nonclinical”, “summaries”, and “regional”
Each of these attributes works the same way and will be describe in this single section. Each attribute corresponds to a single module of the application. When a submission to the application contains application module information corresponding to this attribute, the attribute value is “true”. When information corresponding to this attribute is not provided in the submission, the attribute is not used in the <submission> element referencing it and its assumed value is “false”. Building on the previous example, a submission with information in the quality module and in the efficacy module but in no other module might look the following way:

<submission quality=“true” clinical=“true” type=“I” serialNumber= “0002” date=“2000-06-28” code=“amendment 2”/>

B. Specifications for the module TOC files

There is a separate TOC file for each module of the application (regional, summary, quality, nonclinical, clinical). Each module TOC files include a complete list of all files provided for that module. The elements and attributes provide information for a hypertext link to the specific file. Since the information in the module TOC file is cumulative and each newly submitted module TOC file would replace the previously submitted TOC file for that specific module. A summary of the elements and attributes for the module files is in Table 3.

Table 3: Elements and attributes for each module file

<toc>	Organizes the module
“module”	Name of module toc
<heading>	Toc headings to organize the files
“title”	Title for heading used in the TOC
“category”	Category of heading
<document>	One element for each document and dataset submitted
“ link”	Part of hypertext link to file - Path to file including filename and section subfolders
“submissionCode”	Part of hypertext link to file - code to name of submission date folder
“status”	Status of file whether current, withdrawn or replaced
“updates”	Name of file and submissioncode for file being updated
“subcategory”	Type of document
“keywords”	Keyword to help sort and identify file

The top three lines of each TOC file contain the declaration. These lines are provided below just as they should appear in each TOC file comprising the CTOC:

```
<?xml version="1.0"?>
<?xml:stylesheet type="text/xsl"
href="http:\\www.fda.gov\cder\XML_Resource\CTOC\toc_v001.xsl"?>
<!DOCTYPE toc SYSTEM "
http:\\www.fda.gov\cder\XML_Resource\CTOC\toc_v003.dtd">
```

The names, order and number of occurrence of elements in each module TOC file are controlled by the DTD referenced in the declaration. The names, order and number of occurrences for each element are also provided here with a description of element content. The attributes for each element are described with the element.

1. *Element <toc>*

This is the root element and it contains all the other elements in the TOC file. It has no other content and occurs only once. Its end tag (</toc>) marks the end of the TOC file. The <toc> element has one attribute called "module", described below.

a) Attribute <toc> "module"

The value of the "module" attribute is the application module for which this TOC file is the subject: Regional, summary, quality, nonclinical, clinical. The value of the module attribute is the text that will be displayed in the browser in reference to this TOC.

2. *Element <heading>*

This element creates a heading within the browser to organize the list of files in the TOC. The <heading> element can contain other child or nested elements such as other <heading> elements or <document> elements, or it can be empty. It has no other content. The <heading> element has two attributes: "title" and "category".

a) Attribute <heading> "title"

The value of this attribute is used to name the <heading> element that is displayed to the CTOC user. It is an alphanumeric string and has no other limits.

b) Attribute <heading> "category"

The value of the "category" attribute is used to organize the files in the CTOC. The "category" attribute value is one of the alphanumeric strings listed in the DTD. Every heading element has a "category" attribute. The allowed values for the "category"

attribute are provided in "Section C" of this document. They are based on the International Conference on Harmonization (ICH) Common Technical Document (CTD).

3. Element <document>

There is one <document> element for each file submitted to the application. There is no limit to the number of <document> elements within a <heading> element. The <document> element content is the text that names this element to the user of the CTOC.

For example, in the TOC file for the clinical module, a file called bioequivalence data is included under the "heading" called "Bioequivalence" which is nested in the "heading" called "HPBio". The file (without any file location information) may appear as follows:

```
<toc module="clinical">
   <heading title="HPBio" category=" Clinical.Biopharm.BABE">
      <heading title="Bioequivalence" category="
      Clinical.Biopharm.BABE.BE.Comparative.BA">
         <document>Bioequivalence Data </document>
      </heading>
   </heading>
</toc>
```

When new files are submitted, they would be placed with the previous files, using the same <heading> elements. Do not create a new <heading> element to hold the new or old files.

The <document> element has seven attributes: "status", "updates", "subcategory", "keywords", "link" and "submissionCode".

a) Attribute <document> "link"

The value of the "link" attribute is the complete filename of file referenced in this <document> element. The file may have any name as long as it is accurately referenced as the value of this attribute. The complete filename includes subfolders used inside the submission folder. The section folders are described in attachment 1. For example, if you place a file named *study123.pdf* inside a folder named *pneumonia* in the "0000" folder, the "link" attribute value would be */pneumonia/study123.pdf*.

The "link" and "submission" attributes together provide the information used to create hyperlinks to the file referenced in the <document> element.

b) Attribute <document> “submissionCode”
The “submissioncode” attribute provides the date portion of a link. The value of this attribute is a code selected by you and associated with a <submission> “date” attribute. When the code selected by you appears as the contents of a <submission> element it is associated with the “date” attribute in that element.

Building on the previous example, TOC reference to the bioequivalence data file may appear as follows:

```
<toc module=“clinical”>
   <heading title=“HPBio” category=“ Clinical.Biopharm.BABE”>
      <heading title=“Bioequivalence” category=“
      Clinical.Biopharm.BABE.BE.Comparative.BA”>
         <document link=“bioequvalence001.xpt”
         submissionCode=“original”> Bioequivalence Data
         File</document>
      </heading>
   </heading>
</toc>
```

c) Attribute <document> “status”
This attribute indicates the status of the file being referenced in this element. It has one of three values: “current”, “amended”, “replaced” and “withdrawn”. The meaning of these values is provided in Table 4.

Table 4 Definitions for File Status

<document> “status” value	Description
current	The file is current regardless of whether it is in this submission or in a previous submission. If the <document> “status” attribute is not used it is assumed to be current.
amended	Additions were made to the file or it has been changed
replaced	The file has been replaced in another submission.
withdrawn	The file is no longer considered to be part of the current application and it has not been replaced.

d) Attribute <document> “updates”
There are occasions when a submission will contain a file that is intended to replace, add to, change or withdraw a previously submitted file. In this case the value of the “replaces” attribute is the filename of the old file followed by a comma which is followed by the “submissioncode” attribute value for the old file. The filename includes the extension and subfolder path (subordinate to the serial numbered file) of the old file.

When a submission to the application replaces a previously submitted file, the <document> element that references the new file should be placed within the same <heading> element containing the old file's <document> element. That is, don't create a new <heading> element to hold the new or the old files.

Building on the previous example, the TOC reference to a submission of a replacement bioequivalence file may appear as follows:

```
<toc module="clinical">
  <heading title="HPBio" category=" Clinical.Biopharm.BABE">
        <heading title="Bioequivalence" category="
        Clinical.Biopharm.BABE.BE.Comparative.BA">
              <document
              link="bioequvalence001.xpt"submissioncode="orig
              inal" section="&V2;"
              status="replaced">Bioequivalence Data
              File</document>

              <document link="bioequvalence002.xpt"
              submissioncode="amendment_2" section="&V2;"
              replaces="bioequivalence001.xpt,original"> New
              Bioequivalence Data File</document>
        </heading>
  </heading>
</toc
```

e) Attribute <document> “keywords”
The “keywords” attribute is used to provide more information about the file being referenced by the <document> element. This information is a list of alphanumeric strings (words) separated by a comma. The value of each string can be any alphanumeric string that does **not** start with a number.

A list of potential “keyword” attribute value subjects with descriptions is in the following table:

Table 5 Keywords

examples of <document> “keyword” attribute value subjects	Description
Study ID	A unique identifier for the study and related files or batches
Batch Use	For batch records, indicate if the batch was used in a clinical, bioequivalence, pharmtox or stability study.

f) Attribute <document> “subcategory”
The value of the “subcategory” attribute allows the CTOC user to sort the file references in a module TOC within the heading structure. The “subcategory” attribute value can be one of the values allowed in the DTD. The allowed values are listed in “Section D” with short description of their use.

C. Values for category attribute

The value of the “category” attribute is used to help the CTOC user sort the file references in a module’s TOC. The “category” attribute is a code that is associated with a specific part of the drug application submission. The “category” attribute is required for each <folder> and each <document> element. These codes are listed in the category dtd named “category_v500.dtd”. A copy of the list is provided here starting on the next page:

```
<!-- category entities used as values for the category attribute -->

<!ENTITY % a.RL          'Regional.Administrative.Prescribing.Annual.Report.Reports.Summary.Summaries|
                          Regional.Administrative.Prescribing.Certification.Certifications|
                          Regional.Administrative.Prescribing.Form.Forms|
                          Regional.Administrative.Prescribing.Labeling.Label.Labels.Viewing.Printed.Graphic.Only|
                          Regional.Administrative.Prescribing.Labeling.Label.Labels.Text|
                          Regional.Administrative.Prescribing.Labeling.Label.Labels.Container.Investigators|
                          Regional.Administrative.Prescribing.Other'>
<!ENTITY % a.SL          'Summary.Quality.Chemistry.CMC.Overall|
                          Summary.Nonclinical.Safety.Pharm.Tox.PharmTox.Overview.Clinical|
                          Summary.Nonclinical.Safety.Pharm.Tox.PharmToxOverview.Written|
                          Summary.Nonclinical.Safety.Pharm.Tox.PharmToxOverview.Tabulated|
                          Summary.Clinical.PharmacokineticPK.PharmacodynamicPD.Biopharm.BABE.BE.ComparativeBA|
                          Summary.Clinical.Microbiology'>
<!ENTITY % a.QL          'Quality.Chemistry.CMC.Substance.Active.API|
                          Quality.Chemistry.CMC.Substance.Active.API.General.S1|
                          Quality.Chemistry.CMC.Substance.Active.API.Manufacture.Processing.Synthesis.S2|
```

Quality.Chemistry.CMC.Substance.Active.API.Characterization.Elucidation.S3|

Quality.Chemistry.CMC.Substance.Active.API.Tests.Control.Specification.Specifications.S4|

Quality.Chemistry.CMC.Substance.Active.API.Reference.Standards.Working.Material.Materials.S5|

Quality.Chemistry.CMC.Substance.Active.API.Container.Closure.Packaging.S6|

Quality.Chemistry.CMC.Substance.Active.API.Stability.S7|

Quality.Chemistry.CMC.Product.Products|

Quality.Chemistry.CMC.Product.Products.Description.Composition.Formulation.Components.P1|

Quality.Chemistry.CMC.Product.Products.Pharmaceutical.Development.One.Time.Tests.P2|

Quality.Chemistry.CMC.Product.Products.Manufacture.Processing.P3|

Quality.Chemistry.CMC.Product.Products.Tests.Controls.Specification.Specifications.Excipients.P4|

Quality.Chemistry.CMC.Product.Products.Tests.Controls.Specification.Specifications.Only.P5|

Quality.Chemistry.CMC.Product.Products.Reference.Standard.Standards.Working.Material.Materials.P6|

Quality.Chemistry.CMC.Product.Products.Container.Closure.Packaging.P7|

Quality.Chemistry.CMC.Product.Products.Stability.P8|

Quality.Chemistry.CMC.Appendix.Appendices|

Quality.Chemistry.CMC.Appendix.Appendices.Facilities.Facility.Equipment|

Quality.Chemistry.CMC.Appendix.Appendices.Facilities.Facility.Equipment|

Quality.Chemistry.CMC.Regional|

Quality.Chemistry.CMC.Regional.Batch.Record.Records.Executed|

Quality.Chemistry.CMC.Regional.Methods.Validations.Verifications.Package.Packages|

Quality.Chemistry.CMC.Regional.Comarability.Protocol.Protocols'>

<!ENTITY % a.NL 'Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacology.I|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacology.I.Overview.I.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacology.I.Overview.I.1.Primary.Pharmacodynamics.I.1.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacology.I.Overview.I.1.Secondary.Pharmacodynamics.I.1.2|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacology.I.Overview.I.1.Safety.Pharmacology.I.1.3|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacology.I.Pharmacodynamic.Drug.Interaction.Interactions|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Overview.2.A|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Method.Methods.Methodology.Methodologies.Validation.Validations.2.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Distribution.2.3.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Metabolism.InVivo.In.Vivo.2.4.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Metabolism.InVitro.In.Vitro.2.4.2|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Absorption.Single.Dose.2.2.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Absorption.Repeated.Doses.2.2.2|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Protein.Binding.II.2.3.2|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Pregnant.Nursing.2.3.3|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Other.Distribution.2.3.4|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Possible.Metabolic.Pathway.Pathways.2.4.3|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Induction.Inhibition.Enzyme.Enzymes.2.4.4|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Excretion.2.5.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Analytical.Methods.Validations.2.1.Excretion.Bile.2.5.2|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Drug.Drug.Interactions.2.5|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Other.2.6|

Nonclinical.Safety.Pharm.Tox.PharmTox.Pharmacokinetics.II.Kinetics|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Overview.3.A|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Overview.Toxicokinetics.Study.Studies.3.B|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Overview.Toxicokinetics.Data.3.C|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Overview.Drug.Substance.3.D|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Single.Dose.3.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Single.Dose.3.1.Species|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Single.Dose.3.1.Species.Route|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Repeat.Dose.NonPivotal.3.2.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Repeat.Dose.NonPivotal.3.2.1.Species|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Repeat.Dose.NonPivotal.3.2.1.Species.Route|

NonclinicalSafetyPharmTox.ToxicologyIII.RepeatDosePivotalOnly322|

NonclinicalSafetyPharmTox.ToxicologyIII.RepeatDosePivotalOnly322.Species|

NonclinicalSafetyPharmTox.ToxicologyIII.RepeatDosePivotalOnly322.Species.Route|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Repeat.Dose.Pivotal.Only.3.2.2|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Repeat.Dose.Pivotal.Only.3.2.2.Species|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Repeat.Dose.Pivotal.Only.3.2.2.Species.Route|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Genotoxicity.In.Vitro.InVitro.3.3.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Genotoxicity.In.Vivo.InVivo.3.3.2|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Carcinogenicity.Long.3.4|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Carcinogenicity.Short.3.4|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Carcinogenicity.Other.3.4|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Reproduction.Non.Pivotal.3.5.1|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Fertility.Early.Embryonic.3.5.2|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Embryo.Fetal.3.5.3|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Prenatal.Postnatal.Maternal.3.5.4|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Local.Tolerance.3.6|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Other.3.7|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Other37.Antigenicity|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Other37.Immunotoxicity|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Other37.Mechanistic|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Other37.Dependence|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Other37.Metabolite.Metabolites|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Other37.Impurity.Impurities|

Nonclinical.Safety.Pharm.Tox.PharmTox.Toxicology.III.Key.References.Publication.Publications'>

<!ENTITY % a.CL 'Clinical.Biopharm.BABE|

Clinical.Biopharm.BABE.BA.Bioavailability|

Clinical.Biopharm.BABE.BE.Comparative.BA|

Clinical.Biopharm.BABE.Invivo.Invitro.Correlation.Correlations|

Clinical.Biopharm.BABE.Bio.Analytical|

Clinical.Human.Biomaterial.Biomaterials|

Clinical.HumanBiomaterials.Plasma.Protein.Binding|

Clinical.HumanBiomaterials.Hepatic.Metabolism.Interaction.Interactions|

Clinical.HumanBiomaterials.Other|

Clinical.Pharmacokinetic.PK|

Clinical.Pharmacokinetic.PK.Healthy.Tolerability|

Clinical.Pharmacokinetic.PK.Patient.Tolerability|

Clinical.Pharmacokinetic.PK.Intrinsic.Factor.Factors|

Clinical.Pharmacokinetic.PK.Extrinisic.Factor.Factors|

Clinical.Pharmacokinetic.PK.Population|

Clinical.Pharmacodynamic.PD|

Clinical.Pharmacodynamic.PD.Healthy.PKPD|

Clinical.Pharmacodynamic.PD.Patient.PKPD|

Clinical.Efficacy.Safety|

Clinical.Efficacy.Safety.INDICATION|

Clinical.Efficacy.Safety.INDICATION.Controlled.Trial.Trials|

Clinical.Efficacy.Safety.INDICATION.Controlled.Trial.Trials.Study.Studies.Report.Reports|

Clinical.Efficacy.Safety.INDICATION.Controlled.Trial.Trials.Protocol.Protocols.Amendment.Amendments|

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Clinical.Efficacy.Safety.INDICATION.Uncontrolled.Trial.Trials|

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Clinical.Efficacy.Safety.INDICATION.Other|

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Clinical.Patient.Listing.Listings.CRF.CRFs|

Clinical.Key.References.Publication.Publications|

Clinical.Integrated.Summary.Efficacy.ISE|

Clinical.Integrated.Summary.Safety.ISS|

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<!ENTITY % a.ML 'Clinical.Microbiology|

Clinical.Microbiology.AntiInfective|

Clinical.Microbiology.AntiInfective.Key.References.Publication.Publications|

Clinical.Microbiology.AntiInfective.General.Characterize.Characterization|

Clinical.Microbiology.AntiInfective.Provisional.Breakpoint.Breakpoints|

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Clinical.Microbiology.AntiInfective.Clinical.Breakpoint.Breakpoints|

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Clinical.Microbiology.AntiViral|

Clinical.Microbiology.AntiViral.In.Vivo.In.Vitro.InVivo.InVitro.Preclinical.Methodology.Methodologies|

Clinical.Microbiology.AntiViral.Mechanism|

Clinical.Microbiology.AntiViral.Spectrum|

Clinical.Microbiology.AntiViral.Resistance|

Clinical.Microbiology.AntiViral.Drug.Interaction.Interactions|

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Clinical.Microbiology.AntiViral.In.Vivo.InVivo.Laboratory.Methodology.Methodologies|

Clinical.Microbiology.AntiViral.Viral.Load.Assay.Specification.Specifications|

Clinical.Microbiology.AntiViral.Viral.Load.Data|

Clinical.Microbiology.AntiViral.Cross.Resistance|

Clinical.Microbiology.AntiViral.Miscellaneous|

Clinical.Microbiology.AntiViral.Virologic.Immunologic.Measurement.Measurements'>

D. Values for subcategory attributes

The "subcategory" attribute occurs in the <document> element. It is used to sort <document> elements within the <folder> element and to reorganize them outside the <folder> element.

The value of the "subcategory" attribute is limited to the list of values in the TOC file's DTD. All the "subcategory" values can be used in any module, but they are intended for use in the modules listed with them in the table below:

<document> "subcategory" value	Used in this module	Used in the <document> element for These CTOC File References
cover_letter	all modules	Used for a cover letter regardless of where it occurs
dataset	all modules	Datasets except for CRT files regardless of the software format (The study ID should be part of the <document> element content)
establishment	all modules	Establishment description
impurities	all modules	Files related to impurity descriptions, specifications and studies
other	all modules	Other
publication	all modules	Publication copies and references
summary	all modules	Summary reports and written summaries except for integrated summaries
CRF	Clinical	All case report forms
investigator	Clinical	Investigator Information
ISR	Clinical	Individual Safety Report
profiles	Clinical	Patient profiles
amendment	Clinical Nonclinical	Protocol Amendments (The protocol ID should be part of the <document> element content)
protocol	Clinical Nonclinical	Protocols (The protocol ID should be part of the <document> element content)
study_reports	Clinical Nonclinical	Study Reports (The study ID should be part of the <document> element content)
waiver	Clinical Quality	All waiver documentation
analytical	Quality	Analytical procedures and methodologies
container_closure	Quality	Quality module container/closure overview and summary files
formulation	Quality	Quality module drug product formulation
process	Quality	Quality module manufacturing process descriptions for drug product and for drug substance
special	Quality	Novel excipient and human or animal source excipient descriptions and SPOTS database files and excipient descriptions
specification	Quality	Drug Product, In-process, and Raw Material specifications

<document> "subcategory" value	Used in this module	Used in the <document> element for These CTOC File References
stability	Quality	Quality module stability data files
validation	Quality	Procedure validations, verification and validation packages
1571	Regional	FDA form 1571
2252	Regional	FDA form 2252
356h	Regional	FDA form 356h
ARI	Regional	Annual report information
copy_cert	Regional	Field copy certification
debarment	Regional	Debarment certifications
DL	Regional	Draft Labeling
EDR	Regional	Electronic Document Room Meta Data for each submission
financial	Regional	Financial disclosure
FPL	Regional	Final Printed Labeling
LOA	Regional	Letters of Authorization
patent	Regional	Used for all patent information and certification documents
PCR	Regional	Commitment Report (PM)
user_fee	Regional	User fee cover sheet