# *The eCTD Backbone File Specification for Modules 2 through 5*

Revision History

| Date | Version | Summary of Changes |
|---|---|---|
| 2003-08-13 | 1.0 | Original version |
| 2004-03-11 | 1.1 | Clarifications to the original version |
| | | |

# The eCTD Backbone Files Specification for Modules 2 through 5 (Module 2 to 5 eCTD Backbone File)

This document provides specifications for creating the electronic common technical document (eCTD) backbone file for modules 2 to 5 of the common technical document (CTD) for use with the guidance to industry: *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Applications and Related Submissions.*

The Module 2 to 5 eCTD Backbone File includes information for each file submitted in modules 2 to 5. The file information is provided within an XML element called the *leaf* element. The *leaf* elements are organized using the CTD headings. The CTD headings are named and organized according to the subject matter of the information contained in the file. The heading information is provided in an XML element called heading elements.

Because the Module 2 to 5 eCTD Backbone File may be used in a wide range of applications and related submission types, a specific submission will not use all of the possible heading elements. You should only include the heading elements needed to organize the files in your submission.

## I. START AND FINISH OF THE MODULE 2 TO 5 ECTD BACKBONE FILE

You should name the Module 2 to 5 eCTD Backbone File *index.xml* and place it in the main submission folder as described in *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Applications and Related Submissions*. For example, the path for the *index.xml* for sequence number 0006 is ../0006/index.xml.

The header contains the root element, <ectd:ectd> and the last element, </ectd:ectd>[1] of the Module 2 to 5 eCTD Backbone File. This is always the same. The header contains information about the following:

1. Version of XML being used
2. Type of characters that are allowed in the file
3. Location of the standards that control the organization of the eCTD backbone files
4. Organization element and Leaf element for the Module 1 eCTD Backbone File
5. Indication that the file information is ended (end tag)

A sample of the header and the last line of the Module 2 to 5 eCTD Backbone File is provided below:

```
<?xml version = "1.0" encoding = "UTF-8"?>
<!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-3-0.dtd">
        <ectd:ectd
                xmlns:ectd = "http://www.ich.org/ectd"
                xmlns:xlink = "http://www.w3c.org/1999/xlink">
```

[1] This is the end tag for the root element.

```
        <!--All the heading elements and content for module 2, 3, 4, and module 5
        will be provided after these elements and before the last element closing
        tag named </ectd:ectd> -->
</ectd:ectd>
```

The elements used to organize files for Modules 2 to 5 are placed within the area represented by the comment in the example shown above. Information about creating those elements is provided in other sections of this specification.

## II. LEAF ELEMENT

Information for an individual file is contained in the *leaf* element, its attributes and its *title* element. The *leaf* element is used repeatedly throughout the eCTD backbone file to provide individual information for each submitted file.

The table below provides the name of each part of the *leaf* element and a brief indication of its purpose:

| Part of "leaf" Element | Purpose of *leaf* Element Part |
|---|---|
| <leaf> | Tag indicating start of leaf element to organize the information for . each submitted file. |
| ID | This attribute provides a unique identification of the leaf element in the submission. |
| operation | This attribute provides information about the life cycle of the leaf. |
| modified-file | This attribute provides the ID of a previously submitted leaf that is effected by the operation attribute in the current submission, if applicable . |
| checksum | This attribute provides the document's checksum value (Also known as document's "hash"). |
| checksum-type | This attribute provides the type of checksum that is in the checksum attribute. ICH currently uses a 128 bit checksum or “message digest” generated by the MD5 algorithm. |
| xlink:href | This attribute provides the location of the file using the file’s path. |
| xlink:show | This attribute has not yet been defined within ICH |
| title | This element provides the title of the document to help the reader identify the subject matter. Do not include information in the title already in other areas of the backbone files in the title e.g., application number, heading names). |
| </leaf> | Tag indicating end of leaf element. |

The following is an example of the leaf element for a file containing the first version of the tabular listing of all clinical studies provided in module 5.

```
<leaf >
        ID="a1234567"
        operation="new"
```

```
        modified-file=""
        checksum="9f52fcd71d726c74faf07c85d46b3363"
        checksum-type="md5"
        xlink:href="m5/tabular-listing-of-studies.pdf"
        <title>Tabular listing of all clinical studies</title>
</leaf>
```

For the remainder of this section each part of the leaf element is described in detail in its own subsection.

### A. Start Tag for the leaf Element

The purpose of the start tag is to provide a machine-readable indication that file information is beginning. All the *leaf* element attributes and the *title* element are contained between the leaf start tag and the leaf end tags.

The start tag for the *leaf* element begins with the "less than" symbol, "<", and the lower case word "leaf". This is followed by each of the *leaf* element attributes and their values. The *leaf* element, its attributes and their values are placed between the word "leaf" and the closing "greater than" symbol of the *leaf* element start tag.

The *leaf* element start tag and its matching end tag with all the attribute and element contents are used for each file being submitted, modified or referenced[2] to the Agency for review. The *leaf* element is the fundamental block of information for every file and occurs in both the Module 2 to 5 eCTD Backbone File and Module 1 eCTD Backbone File.

### B. ID Attribute for leaf Element

The purpose of the *leaf* element *ID* attribute is to provide a unique identification for the file within the submission. This facilitates referencing from other submissions. The *leaf* element *ID* combined with the application number, sequence number and name of the eCTD backbone file provide a unique ID for the file.

The *ID* attribute occurs after the word "leaf" and begins with the upper case letters "ID". The value for the *ID* attribute is provided in a statement that begins with the equal sign and quotation mark, (="), followed by the *ID* attribute value ending with a quotation mark. There should be no spaces in the *ID* attribute value statement.

The *ID* value must start with a letter followed by a combination of letters and numbers to provide a unique identification of this leaf element within the Module 2 to 5 eCTD Backbone File. Examples of valid ID attributes:

[2]Including previously submitted information. See *Guidance to Industry: Providing Regulatory Submissions in Electronic Format — Human Drug Applications and Related Submissions* for more information.

ID="a1234567"
ID=”id12235”
ID=”pid1234”

The following are invalid values for the *ID* attribute:

ID=”123a456” - does not start with a letter
ID=”1234567” - does not have a letter
ID=”a 1246” - includes a space

You should provide an *ID* attribute and value for each *leaf* element that is unique for the submission.

### C. Operation attribute for the leaf element

The purpose of the *operation* attribute is to provide a machine-readable indication of the effect this *leaf* has on a *leaf* included in previously submitted eCTD backbone files.

You should include an *operation* attribute for each *leaf* you are submitting. The value for the operation attribute is limited to: *new*, *append*, *replace*, and *delete*. The table below summarizes the meaning of each modified-file attribute value.

| Attribute and Value | Meaning |
|---|---|
| operation ="new" | This means that the leaf does not have an effect on a *leaf* included in previously submitted eCTD backbone files. |
| operation ="append" | This means that the file contained in the current *leaf* provides information that is in addition to information in a file contained in a *leaf* previously submitted eCTD backbone file. If there are a series of files appending an original file, only append the original file. You should not append a file that append another file. |
| operation ="replace" | This means the file contained in the current *leaf* replaces a file contained in a *leaf* in a previously submitted eCTD backbone file. |
| operation ="delete" | This means a file contained in a *leaf* in a previously submitted eCTD backbone file should no longer be considered in the evaluation of the application. In this situation, there is no file provided for the leaf. |

### D. Modified-file attribute for the leaf element

The purpose of the *modified-file* attribute is to provide the location of *leaf* that is being modified (i.e. appended, replaced, or deleted) by the current *leaf* element. The *modified-file* attribute should have a value when the *operation* attribute has a value of *append*, *replace* or *delete*.

The *modified-file* attribute for the *leaf* element begins with the lowercase hyphenated word "modified-file". The value for the *modified-file* attribute is provided in a statement that begins with the equal sign and quotation mark, (="), followed by the *modified-file* attribute value and

ending with a quotation mark. There should be no spaces in the *modified-file* attribute's value statement.

The *modified-file leaf* attribute should have a value of a relative path and filename with a bookmark. You should use the relative path and filename for the eCTD backbone file (ie., index.xml or us-regional.xml) containing the modified file's leaf element. You should append the modified file's leaf *ID* value to the relative path and file name as a bookmark. This is detailed in the next paragraph.

The relative path and filename for a previously submitted *leaf* will start with two periods and a slash, "../", providing a machine readable instruction to move up one level in the directory structure to where the previous submission folders are located. These characters are followed with the sequence folder name (four numbers, e.g. 0001) and another slash. This is followed by the path and filename for the *leaf* you want to modify. For example, to replace the tabular-listing-studies.pdf file submitted in Module 5 of the original submission associated with the leaf ID value id12345, the *modified-file* attribute value is as follows:

modified-file="../0000/index.xml#id12345 "

**E. checksum attribute for the leaf element**

The purpose of the *checksum* attribute is to provide the value of the checksum for the file this leaf is providing. The checksum is the result of an algorithm that breaks down a file into a unique128 bit "message digest" or "fingerprint". The "fingerprint" is used to verify that the file was transmitted and received without being modified[3].

The *checksum* attribute for the *leaf* element begins with the lowercase word "checksum". The value for the *checksum* attribute is provided in a statement that begins with the equal sign and quotation mark, (="), followed by the *checksum* attribute value and ending with a quotation mark. There should be no spaces in the *checksum* attribute's value statement. An example of a *checksum* attribute and its value is provided:

checksum="e854d3002c02a61fe5cbe92fd97b0018"

You should provide a *checksum* attribute and value for every *leaf* element that includes a file.

**F. checksum-type attribute for the leaf element**

The *checksum-type* attribute provides the name of the algorithm used to produce the checksum value. It should unambiguously identify the algorithm being used.

The *checksum-type* attribute for the *leaf* element begins with the lowercase hyphenated word "checksum-type". The value for the *checksum-type* attribute is provided in a statement that begins with the equal sign and quotation mark, (="), followed by the checksum-type attribute

[3] Checksum value is also known as the document hash.

value and ending with a quotation mark. There should be no spaces in the *checksum-type* attribute's value statement. An example of a *checksum-type* attribute and its value is provided:

checksum-type="MD5"

You should provide a checksum-type attribute and value for every leaf element that contains a checksum value.

### G. xlink:href attribute for the leaf element

The purpose of the *xlink:href* attribute is to provide the machine-readable location and filename of the file associated with the leaf element. The location is provided as the relative path and filename of the document. The relative path should be provided relative to the eCTD backbone file (i.e., index.xml or us-regional.xml) for the leaf.

The *xlink:href* attribute for the *leaf* element begins with the lowercase hyphenated word "xlink:href". The value for the *xlink:href* attribute is provided in a statement that begins with the equal sign and quotation mark, (="), followed by the *xlink:href* attribute value and ending with a quotation mark. There should be no spaces in the *xlink:href* attribute's value statement. The following is an example of a *xlink:href* attribute and its value for the tabular-listing-studies.pdf in module 5 in the same submission:

xlink:href="m5/tabular-listing-studies.pdf "

When linking to a file in a previous submission to the application use "../" to signify the level of the other submissions of an application. The following is an example of a *xlink:href* attribute and its value for the tabular-listing-studies.pdf in module 5 submitted in an earlier submission (sequence number 0001) in the same application:

xlink:href="../0001/m5/tabular-listing-studies.pdf "

Currently, you cannot link to a file submitted to a different application. However, this capability will be available in the future.

You should provide an *xlink:href* attribute and its value for every *leaf* element that provides a file.

### H. xlink:show attribute

The ICH specification has not yet defined a use for the *xlink:show* attribute and does not need to be included. If you do include this attribute, you should have the value of "none" or "new" (for example., xlink:show="none") for the *xlink:show* attribute.

### I. Title child element of the leaf element

The purpose of the *title* element is to provide a title for the file that is meaningful to the human reader. The title should not include information already provided in the leaf attributes or heading elements (e.g., module number, table of contents numbers). You can use spaces, upper and lower case letters and numbers freely.

The *title* element begins with the "less than" symbol, (<), and the lower case word "title", followed by the "greater than" symbol, (>). The *title* content is provided after the greater than sign. The *title* element is ended similar to how it is started except a slash is placed between the less than symbol and the word “title”. An example of a *title* element and its content is provided:

<title>Tabular listing of all clinical studies </title>

You should provide a *title* element and content for every *leaf* element that provides a file.

### J. End Tag for the leaf Element

The end tag for the *leaf* element is the same as the start tag except that it contains a "/" symbol after the "less than" symbol, (</), used to start the tag. It occurs after the *title* element's end tag and indicates the end of the file information for the *leaf* element.

## III. HEADING ELEMENT

The *leaf* elements in the eCTD backbone file are organized according to the modules and headings and subheadings of the CTD. There is a heading element in the Module 2 to 5 eCTD Backbone File for the CTD headings and many of the subheadings. Each element has a start tag and an end tag. The element tags start with a "less than" symbol, “<”, and end with a "greater than" symbol, “>”. The name of the element is inserted between these symbols. The heading elements are completed with an end tag. The end tag is the same as the start tag except it has a "slash", “/” after the "less than" symbol, (</). The content for the element (i.e., other heading elements and *leaf* elements) occurs between the start tag and the end tag. *Leaf* elements may be provided directly within only certain heading elements. In the following example is an isolated part of the Module 2 to 3 eCTD Backbone File. The heading element m2-common-technical-document-summaries contains the heading element m2-2-introduction. The heading element m2-2-introduction contains the *leaf* element for the CTD-introduction.pdf file.

```
<m2-common-technical-document-summaries>
        <m2-2-introduction>
                <leaf >
                        ID="a1234567"
                        operation="new"
                        checksum=" e854d3002c02a61fe5cbe92fd97b0018"
                        checksum-type="md5"
                        xlink:href="m2/CTD-introduction.pdf"
                        version="Version-1">
                        <title>Introduction to CTD Submission</title>
                </leaf>
```

```
        </m2-2-introduction>
</m2-common-technical-document-summaries>
```

Some of the heading elements in the eCTD backbone file have attributes associated with them to help in organizing the file information. Each of heading element attributes begins after the heading element name with a space followed by the lowercase attribute name. The value for the attribute is provided in a statement that begins with the equal sign and quotation mark, (="), followed by the attribute's value and ending with a quotation mark. There should be no spaces in the attribute's value statement.

Some of the attributes occur for more than one element. You should make sure that the attribute values each of these elements are coordinated so that they are the same when appropriate. The table, below, lists each heading element attribute name and the element or elements where it can occur followed by the same information organized with the heading elements listed and their associated attributes.

| **Attribute Name** | **Applicable Heading Element(s)** |
|---|---|
| substance | <m3-2-s-drug-substance><br><m3-2-a-1-facilities-and-equipment><br><m3-2-a-2-adventitious-agents-safety-evaluation> |
| manufacturer | <m3-2-s-drug-substance><br><m3-2-p-drug-product><br><m3-2-a-1-facilities-and-equipment><br><m3-2-a-2-adventitious-agents-safety-evaluation> |
| product-name | <m3-2-p-drug-product><br><m3-2-a-1-facilities-and-equipment><br><m3-2-a-2-adventitious-agents-safety-evaluation> |
| dosageform | <m3-2-p-drug-product><br><m3-2-a-1-facilities-and-equipment><br><m3-2-a-2-adventitious-agents-safety-evaluation> |
| excipient | <m3-2-p-4-control-of-excipients> |
| indication | <m2-7-3-summary-of-clinical-efficacy><br><m5-3-5-reports-of-efficacy-and-safety-studies> |

| **Heading Element** | **Applicable Attribute(s)** |
|---|---|
| <m2-7-3-summary-of-clinical-efficacy> | indication |
| <m3-2-s-drug-substance> | substance<br>manufacturer |
| <m3-2-p-drug-product> | product-name<br>dosageform<br>manufacturer |
| <m3-2-p-4-control-of-excipients> | excipient |
| <m3-2-a-1-facilities-and-equipment> | manufacturer<br>substance<br>dosageform<br>product-name |

| | |
|---|---|
| <m3-2-a-2-adventitious-agents-safety-evaluation> | manufacturer<br>substance<br>dosageform<br>product-name |
| <m5-3-5-reports-of-efficacy-and-safety-studies> | indication |

Each of the heading element attributes for the eCTD backbone file is described in detail in the section of this appendix associated with the CTD module where the element and its attribute occur.

The heading elements and heading element attributes for modules 2 through 5 are described below.

### A. Heading elements attributes for Module 2

This section describes the heading elements and attribute values relevant to module 2.

#### *1. Heading elements*

The module 2 heading elements are summarized in the following table. In some cases, the CTD may describe more subheadings than appear on this table. Those subheadings should be used as bookmarks within the individual document. Both the start tag and end tag for each heading element are provided. If there are one or more subheadings for the heading, the corresponding element end tag will occur on the table row below the last relevant subheading. The *leaf* element is included to show where the leaf elements should be placed. The details for the *leaf* elements are not shown on this table to keep it clearer. The *leaf* elements should only occur where indicated in this table. A heading element may contain any number of *leaf* elements. If no documents are submitted for a heading, you should omit the element for that heading in the eCTD backbone file.

| Module 2 CTD Heading | heading element (leaf element abbreviated for clarity) |
|---|---|
| Module 2: Common Technical Document (CTD) Summaries | <m2-common-technical-document-summaries> |
| 2.2 CTD Introduction | <m2-2-introduction><br><leaf><br></leaf><br></m2-2-introduction> |
| Module 2: Quality Overall Summary (QOS) | <m2-3-quality-overall-summary><br><leaf><br></leaf><br></m2-3-quality-overall-summary> |
| Module 2: Nonclinical Overview | <m2-4-nonclinical-overview><br><leaf><br></leaf><br></m2-4-nonclinical-overview> |
| Module 2: Nonclinical Written and | <m2-6-nonclinical-written-and-tabulated-summaries> |

| Module 2 CTD Heading | heading element (leaf element abbreviated for clarity) |
|---|---|
| Tabulated Summaries (NWTS) | |
| 2.6.1 Introduction | <m2-6-1-introduction><br><leaf><br></leaf><br></m2-6-1-introduction> |
| 2.6.2 Pharmacology Written Summary | <m2-6-2-pharmacology-written-summary><br><leaf><br></leaf><br></m2-6-2-pharmacology-written-summary> |
| 2.6.3 Pharmacology Tabulated Summary | <m2-6-3-pharmacology-tabulated-summary><br><leaf><br></leaf><br></m2-6-3-pharmacology-tabulated-summary> |
| 2.6.4 Pharmacokinetics Written Summary | <m2-6-4-pharmacokinetics-written-summary><br><leaf><br></leaf><br></m2-6-4-pharmacokinetics-written-summary> |
| 2.6.5 Pharmacokinetics Tabulated Summary | <m2-6-5-pharmacokinetics-tabulated-summary><br><leaf><br></leaf><br></m2-6-5-pharmacokinetics-tabulated-summary> |
| 2.6.6 Toxicology Written Summary | <m2-6-6-toxicology-written-summary><br><leaf><br></leaf><br></m2-6-6-toxicology-written-summary> |
| 2.6.7 Toxicology Tabulated Summary | <m2-6-7-toxicology-tabulated-summary><br><leaf><br></leaf><br></m2-6-7-toxicology-tabulated-summary> |
| End NWTS | </m2-6-nonclinical-written-and-tabulated-summaries> |
| Module 2: Clinical Overview | <m2-5-clinical-overview><br><leaf><br></leaf><br></m2-5-clinical-overview> |
| Module 2: Clinical Summary (CS) | <m2-7-clinical-summary> |
| 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods | <m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods><br><leaf><br></leaf><br></m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods> |
| 2.7.2 Summary of Clinical Pharmacology Studies | <m2-7-2-summary-of-clinical-pharmacology-studies><br></m2-7-2-summary-of-clinical-pharmacology-studies> |
| 2.7.3 Summary of Clinical Efficacy | <m2-7-3-summary-of-clinical-efficacy<br>indication=""> |

| Module 2 CTD Heading | heading element (leaf element abbreviated for clarity) |
|---|---|
| | <leaf><br></leaf><br></m2-7-3-summary-of-clinical-efficacy>[4] |
| 2.7.4 Summary of Clinical Safety | <m2-7-4-summary-of-clinical-safety><br><leaf><br></leaf><br></m2-7-4-summary-of-clinical-safety> |
| 2.7.5 References | <m2-7-5-literature-references><br><leaf><br></leaf><br></m2-7-5-literature-references> |
| 2.7.6 Synopses of Individual Studies | <m2-7-6-synopses-of-individual-studies><br><leaf><br></leaf><br></m2-7-6-synopses-of-individual-studies> |
| End CS | </m2-7-clinical-summary> |
| End CTD Summaries | </m2-common-technical-document-summaries> |

*2. Attribute Values for Module 2 heading Elements*

The heading element for the Summary of Clinical Efficacy heading, <m2-7-3-summary-of-clinical-efficacy>, has an attribute called *indication*. The purpose of the *indication* attribute is to provide human readable abbreviation of the clinical indication being summarized under this heading. If there is more than one indication for which a Summary of Clinical Efficacy (SCE) is being submitted, you should create an additional SCE heading element for each indication. Each SCE heading element should be the same except for the unique *indication* attribute value and *leaf* content. An example of two *indication* attributes and their values within two SCE heading elements is provided:

```
<m2-common-technical-document-summaries>
    <m2-7-clinical-summary>
        <m2-7-3-summary-of-clinical-efficacy indication="pneumonia">
            <leaf></leaf>[5]
        </m2-7-3-summary-of-clinical-efficacy>
        <m2-7-3-summary-of-clinical-efficacy indication="sepsis">
            <leaf></leaf>[6]
        </m2-7-3-summary-of-clinical-efficacy>
    </m2-7-clinical-summary>
</m2-common-technical-document-summaries>
```

[4] See the description of element attributes after this table
[5] Leaf element abbreviated for clarity.
[6] Leaf element abbreviated for clarity.

You should provide an *indication* attribute value for every SCE heading element. There is no limit to the number of SCE heading elements.

### B. Heading elements and attributes for Module 3

This section includes the heading elements and attribution values relevant to module 3.

#### *1. Module 3 heading elements*

The module 3 heading elements are summarized in the following table. In some cases, the CTD may describe more subheadings than appear on this table. Those subheadings should be used as bookmarks within the individual document. Both the start tag and end tag for each heading element are provided. If there are one or more subheadings for the heading, the corresponding element end tag will occur on the table row below the last relevant subheading. The *leaf* element is included to show where the leaf elements should be placed. The details for the *leaf* elements are not shown on this table to keep it clearer. The *leaf* elements should only occur where indicated in this table. A heading element may contain any number of *leaf* elements. If no documents are submitted for a heading, you should omit the element for that heading in the eCTD backbone file.

| Module 3 CTD Heading | eCTD Element |
|---|---|
| Module: 3 Quality | <m3-quality> |
| 3.2 Body of Data | <m3-2-body-of-data> |
| 3.2.S Drug Substance<br>Name<br>Manufacturer | <m3-2-s-drug-substance<br>substance=""<br>manufacturer="">[7] |
| 3.2.S.1 General Information | <m3-2-s-1-general-information> |
| 3.2.S.1.1 Nomenclature | <m3-2-s-1-1-nomenclature><br><leaf><br></leaf><br></m3-2-s-1-1-nomenclature> |
| 3.2.S.1.2 Structure | <m3-2-s-1-2-structure><br><leaf><br></leaf><br></m3-2-s-1-2-structure> |
| 3.2.S.1.3 General Properties | <m3-2-s-1-3-general-properties><br><leaf><br></leaf><br></m3-2-s-1-3-general-properties> |
| End General Information | </m3-2-s-1-general-information> |
| 3.2.S.2 Manufacture | <m3-2-s-2-manufacture> |

[7] See the description of element attributes after this table.

| Module 3 CTD Heading | eCTD Element |
|---|---|
| 3.2.S.2.1 Manufacturers | <m3-2-s-2-1-manufacturer><br><leaf><br></leaf><br></m3-2-s-2-1-manufacturer> |
| 3.2.S.2.2 Description of Manufacturing | <m3-2-s-2-2-description-of-manufacturing-process-and-process-controls><br><leaf><br></leaf><br></m3-2-s-2-2-description-of-manufacturing-process-and-process-controls> |
| 3.2.S.2.3 Control of Materials | <m3-2-s-2-3-control-of-materials><br><leaf><br></leaf><br></m3-2-s-2-3-control-of-materials> |
| 3.2.S.2.4 Controls of Critical Steps and Intermediates | <m3-2-s-2-4-controls-of-critical-steps-and-intermediates><br><leaf><br></leaf><br></m3-2-s-2-4-controls-of-critical-steps-and-intermediates> |
| 3.2.S.2.5 Process Validation and/or Evaluation | <m3-2-s-2-5-process-validation-and-or-evaluation><br><leaf><br></leaf><br></m3-2-s-2-5-process-validation-and-or-evaluation> |
| 3.2.S.2.6 Manufacturing Process Development | <m3-2-s-2-6-manufacturing-process-development><br><leaf><br></leaf><br></m3-2-s-2-6-manufacturing-process-development> |
| End Manufacture | </m3-2-s-2-manufacture> |
| 3.2.S.3 Characterization | <m3-2-s-3-characterisation> |
| 3.2.S.3.1 Elucidation of Structure and other Characteristics | <m3-2-s-3-1-elucidation-of-structure-and-other-characteristics><br><leaf><br></leaf><br></m3-2-s-3-1-elucidation-of-structure-and-other-characteristics> |
| 3.2.S.3.2 Impurities | <m3-2-s-3-2-impurities><br><leaf><br></leaf><br></m3-2-s-3-2-impurities> |
| End Characterization | </m3-2-s-3-characterisation> |
| 3.2.S.4 Control of Drug Substance | <m3-2-s-4-control-of-drug-substance> |

| Module 3 CTD Heading | eCTD Element |
|---|---|
| 3.2.S.4.1 Specification | <m3-2-s-4-1-specification><br><leaf><br></leaf><br></m3-2-s-4-1-specification> |
| 3.2.S.4.2 Analytical Procedures | <m3-2-s-4-2-analytical-procedures><br><leaf><br></leaf><br></m3-2-s-4-2-analytical-procedures> |
| 3.2.S.4.3 Validation of Analytical Procedures | <m3-2-s-4-3-validation-of-analytical-procedures><br><leaf><br></leaf><br></m3-2-s-4-3-validation-of-analytical-procedures> |
| 3.2.S.4.4 Batch Analyses | <m3-2-s-4-4-batch-analyses><br><leaf><br></leaf><br></m3-2-s-4-4-batch-analyses> |
| 3.2.S.4.5 Justification of Specification | <m3-2-s-4-5-justification-of-specification><br><leaf><br></leaf><br></m3-2-s-4-5-justification-of-specification> |
| End Control of Drug Substance | </m3-2-s-4-control-of-drug-substance> |
| 3.2.S.5 Reference Standards or Materials | <m3-2-s-5-reference-standards-or-materials><br><leaf><br></leaf><br></m3-2-s-5-reference-standards-or-materials> |
| 3.2.S.6 Container Closure System | <m3-2-s-6-container-closure-system><br><leaf><br></leaf><br></m3-2-s-6-container-closure-system> |
| 3.2.S.7 Stability | <m3-2-s-7-stability> |
| 3.2.S.7.1 Stability Summary and Conclusions | <m3-2-s-7-1-stability-summary-and-conclusions><br><leaf><br></leaf><br></m3-2-s-7-1-stability-summary-and-conclusions> |
| 3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment | <m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment><br><leaf><br></leaf><br></m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment> |
| 3.2.S.7.3 Stability Data | <m3-2-s-7-3-stability-data><br><leaf><br></leaf><br></m3-2-s-7-3-stability-data> |
| End Stability | </m3-2-s-7-stability> |

| Module 3 CTD Heading | eCTD Element |
|---|---|
| End Drug Substance | </m3-2-s-drug-substance> |
| 3.2.P Drug Product<br>Name<br>Dosage Form<br>Manufacturer | <m3-2-p-drug-product<br>product-name=""<br>dosageform=""<br>manufacturer="">[8] |
| 3.2.P.1 Description and Composition of the Drug Product | <m3-2-p-1-description-and-composition-of-the-drug-product><br></m3-2-p-1-description-and-composition-of-the-drug-product> |
| 3.2.P.2 Pharmaceutical Development | <m3-2-p-2-pharmaceutical-development><br><leaf><br></leaf><br></m3-2-p-2-pharmaceutical-development> |
| 3.2.P.3 Manufacture | <m3-2-p-3-manufacture> |
| 3.2.P.3.1 Manufacturers | <m3-2-p-3-1-manufacturers><br><leaf><br></leaf><br></m3-2-p-3-1-manufacturers> |
| 3.2.P.3.2 Batch Formula | <m3-2-p-3-2-batch-formula><br><leaf><br></leaf><br></m3-2-p-3-2-batch-formula> |
| 3.2.P.3.3 Description of Manufacturing Process and Process Controls | <m3-2-p-3-3-description-of-manufacturing-process-and-process-controls><br><leaf><br></leaf><br></m3-2-p-3-3-description-of-manufacturing-process-and-process-controls> |
| 3.2.P.3.4 Controls of Critical Steps and Intermediates | <m3-2-p-3-4-controls-of-critical-steps-and-intermediates><br><leaf><br></leaf><br></m3-2-p-3-4-controls-of-critical-steps-and-intermediates> |
| 3.2.P.3.5 Process Validation and/or Evaluation | <m3-2-p-3-5-process-validation-and-or-evaluation><br><leaf><br></leaf><br></m3-2-p-3-5-process-validation-and-or-evaluation> |
| End Manufacture | </m3-2-p-3-manufacture> |
| 3.2.P.4 Control of Excipients | <m3-2-p-4-control-of-excipients<br>excipient="">[9] |

[8] See the description of element attributes after this table.
[9] See the description of element attributes after this table.

| Module 3 CTD Heading | eCTD Element |
|---|---|
| 3.2.P.4.1 Specifications | <m3-2-p-4-1-specifications><br><leaf><br></leaf><br></m3-2-p-4-1-specifications> |
| 3.2.P.4.2 Analytical Procedures | <m3-2-p-4-2-analytical-procedures><br><leaf><br></leaf><br></m3-2-p-4-2-analytical-procedures> |
| 3.2.P.4.3 Validation of Analytical Procedures | <m3-2-p-4-3-validation-of-analytical-procedures><br><leaf><br></leaf><br></m3-2-p-4-3-validation-of-analytical-procedures> |
| 3.2.P.4.4 Justification of Specifications | <m3-2-p-4-4-justification-of-specifications><br><leaf><br></leaf><br></m3-2-p-4-4-justification-of-specifications> |
| 3.2.P.4.5 Excipients of Human or Animal Origin | <m3-2-p-4-5-excipients-of-human-or-animal-origin><br><leaf><br></leaf><br></m3-2-p-4-5-excipients-of-human-or-animal-origin> |
| 3.2.P.4.6 Novel Excipients | <m3-2-p-4-6-novel-excipients><br><leaf><br></leaf><br></m3-2-p-4-6-novel-excipients> |
| End Control of Excipients | </m3-2-p-4-control-of-excipients> |
| 3.2.P. 5 Control of Drug Product | <m3-2-p-5-control-of-drug-product> |
| 3.2.P.5.1 Specifications | <m3-2-p-5-1-specifications><br><leaf><br></leaf><br></m3-2-p-5-1-specifications> |
| 3.2.P.5.2 Analytical Procedures | <m3-2-p-5-2-analytical-procedures><br><leaf><br></leaf><br></m3-2-p-5-2-analytical-procedures> |
| 3.2.P.5.3 Validation of Analytical Procedures | <m3-2-p-5-3-validation-of-analytical-procedures><br><leaf><br></leaf><br></m3-2-p-5-3-validation-of-analytical-procedures> |
| 3.2.P.5.4 Batch Analyses | <m3-2-p-5-4-batch-analyses><br><leaf><br></leaf><br></m3-2-p-5-4-batch-analyses> |

| Module 3 CTD Heading | eCTD Element |
|---|---|
| 3.2.P.5.5 Characterization of Impurities | <m3-2-p-5-5-characterisation-of-impurities><br><leaf><br></leaf><br></m3-2-p-5-5-characterisation-of-impurities> |
| 3.2.P.5.6 Justification of Specifications | <m3-2-p-5-6-justification-of-specifications><br><leaf><br></leaf><br></m3-2-p-5-6-justification-of-specifications> |
| End Control of Drug Product | </m3-2-p-5-control-of-drug-product> |
| 3.2.P.6 Reference Standards or Materials | <m3-2-p-6-reference-standards-or-materials><br><leaf><br></leaf><br></m3-2-p-6-reference-standards-or-materials> |
| 3.2.P.7 Container Closure System | <m3-2-p-7-container-closure-system><br><leaf><br></leaf><br></m3-2-p-7-container-closure-system> |
| 3.2.P.8 Stability | <m3-2-p-8-stability> |
| 3.2.P.8.1 Stability Summary and Conclusion | <m3-2-p-8-1-stability-summary-and-conclusion><br><leaf><br></leaf><br></m3-2-p-8-1-stability-summary-and-conclusion> |
| 3.2.P.8.2 Postapproval Stability Protocol and Stability Commitment | <m3-2-p-8-2-post-approval-stability-protocol-and-stability-commitment><br><leaf><br></leaf><br></m3-2-p-8-2-post-approval-stability-protocol-and-stability-commitment> |
| 3.2.P.8.3 Stability Data | <m3-2-p-8-3-stability-data><br><leaf><br></leaf><br></m3-2-p-8-3-stability-data> |
| End Stability | </m3-2-p-8-stability> |
| End Drug Product | </m3-2-p-drug-product> |
| 3.2.A APPENDICES | <m3-2-a-appendices> |
| 3.2.A.1 Facilities and Equipment | <m3-2-a-1-facilities-and-equipment<br>manufacturer=""<br>substance=""<br>dosageform=""<br>product-name="">[10]<br><leaf><br></leaf><br></m3-2-a-1-facilities-and-equipment |

[10] See the description of element attributes after this table.

| Module 3 CTD Heading | eCTD Element |
|---|---|
| 3.2.A.2 Adventitious Agents Safety Evaluation | <m3-2-a-2-adventitious-agents-safety-evaluation<br>manufacturer=""<br>substance=""<br>dosageform=""<br>product-name="">[11]<br><leaf><br></leaf><br></m3-2-a-2-adventitious-agents-safety-evaluation> |
| 3.2.A.3 Novel Excipients | <m3-2-a-3-excipients><br><leaf><br></leaf><br></m3-2-a-3-excipients> |
| End Appendices | </m3-2-a-appendices> |
| 3.2.R REGIONAL INFORMATION | <m3-2-r-regional-information><br><leaf><br></leaf><br></m3-2-r-regional-information> |
| End Body of Data | </m3-2-body-of-data> |
| 3.3 LITERATURE REFERENCES | <m3-3-literature-references><br><leaf><br></leaf><br></m3-3-literature-references> |
| End Quality | </m3-quality> |

*2. Attribute Values for Module 3 heading Elements*

Five of the Module 3 heading elements have attributes. You should provide attribute values for each of these attributes.

*a)* Drug substance attributes

The heading element for the Drug Substance heading, <m3-2-s-drug-substance>, has two attributes, *substance* and *manufacturer*. The purpose of these attributes is to provide text to indicate the drug substance name or names and organizational headings for different manufacturers of the drug substance. These situations are more fully described in the Guidance for Industry M4: The CTD-- Quality document. An example of two Drug Substance heading elements for different manufacturers of the same drug substance is provided:

```
<m3-quality>
    <m3-2-body-of-data>
        <m3-2-s-drug-substance
            substance="Cure All USP"
```

[11] See the description of element attributes after this table.

```
                    manufacturer="China-DMF-999999">
                        <leaf></leaf>[12]
                </m3-2-s-drug-substance>
                <m3-2-s-drug-substance
                    substance=" Cure All USP "
                    manufacturer="Louisiana">
                        <leaf></leaf>[13]
                </m3-2-s-drug-substance>
        </m3-2-body-of-data >
</m3-quality >
```

You should provide *substance* and *manufacturer* attribute values for every Drug Substance heading element. There is no limit to the number of Drug Substance heading elements. There is no limit to the number of *leaf* elements the Drug Substance heading element can contain.

b) Drug product attributes

The heading element for the Drug Product heading, <m3-2-p-drug-product>, has three attributes, *product-name*, *dosageform* and *manufacturer*. The purpose of these attributes is to provide text to indicate the drug product names and organizational headings for different dosage forms and the organizational headings for different manufacturers of the drug product. These situations are more fully described in the Guidance for Industry M4: The CTD-- Quality document. An example of two Drug Product heading elements for different manufacturers of the same dosage form and the same product name is provided:

```
<m3-quality>
        <m3-2-body-of-data>
                <m3-2-p-drug-product
                    product-name="Cure All"
                    dosageform="Injection"
                    manufacturer="China Plant 1 DMF-0000001">
                        <leaf></leaf>[14]
                </ m3-2-p-drug-product >
                <m3-2-p-drug-product
                    product-name="Cure All"
                    dosageform="Injection"
                    manufacturer="Puerto Rico Internal-Plant-#2">
                        <leaf></leaf>[15]
                </m3-2-p-drug-product>
        </ m3-2-body-of-data >
</m3-quality >
```

[12] Leaf element abbreviated for clarity.
[13] Leaf element abbreviated for clarity.
[14] Leaf element abbreviated for clarity.
[15] Leaf element abbreviated for clarity.

You should provide *product-name*, *dosageform* and *manufacturer* attribute values for every Drug Product heading element. There is no limit to the number of Drug Product heading elements. There is no limit to the number of *leaf* elements the Drug Product heading element can contain.

c) Excipient Attribute

The heading element for Control of Excipients, <m3-2-p-4-control-of-excipients>, has an attribute called *excipient*. The purpose of the *excipient* attribute is to provide text to indicate the excipient for which information is being provided. If there is more than one excipient, you should create an additional Control of Excipients heading element for each excipient. An example of a Control of Excipients element with its *excipient* attribute is provided:

```
<m3-quality>
    <m3-2-p-drug-product
            product-name="Cure All"
            dosageform="Injection"
            manufacturer="China Plant 1 DMF-0000001">
        <m3-2-p-4-control-of-excipients
        excipient="corn syrup">
            <m3-2-p-4-1-specifications>
                <leaf></leaf>[16]
            </m3-2-p-4-1-specifications>
            <m3-2-p-4-2-analytical-procedures>
                <leaf></leaf>[17]
            </m3-2-p-4-2-analytical-procedures>
            <m3-2-p-4-4-justification-of-specifications>
                <leaf></leaf>[18]
            </m3-2-p-4-4-justification-of-specifications>
        </m3-2-p-4-control-of-excipients>
    </m3-2-p-drug-product>
</m3-quality>
```

You should provide an *excipient* attribute value for every Control of Excipients heading element. There is no limit to the number of Control of Excipients heading elements. There is no limit to the number of *leaf* elements the Control of Excipients heading element can contain.

d) Attributes for Appendix Elements

The heading elements for the Facilities and Equipment heading, <m3-2-a-1-facilities-and-equipment> and for the Adventitious Agents Safety Evaluation heading, <m3-2-a-2-

[16] Leaf element abbreviated for clarity.
[17] Leaf element abbreviated for clarity.
[18] Leaf element abbreviated for clarity.

adventitious-agents-safety-evaluation>, have two and three attributes, respectively, from the following 4 possibilities: *manufacturer*, *substance*, *dosageform* and *product-name*. The purpose of these attributes is to provide text to correlate the appendix with the manufacturer, drug substance, dosage form and drug product name. These situations are more fully described in the Guidance for Industry M4: The CTD-- Quality document. An example of the Facilities and Equipment heading and the Adventitious Agents Safety Evaluation heading elements with their attributes is provided:

```
<m3-quality>
    <m3-2-a-appendices>
        <m3-2-a-1-facilities-and-equipment
            manufacturer=" China Plant 1 DMF-0000001"
            product-name="Cure All">
                <leaf></leaf>[19]
        </m3-2-a-1-facilities-and-equipment
        <m3-2-a-2-adventitious-agents-safety-evaluation
            manufacturer="Animal Extractions Inc"
            substance="Parts Substrate"
            dosageform="Injection">
                <leaf></leaf>[20]
        </m3-2-a-2-adventitious-agents-safety-evaluation>
    </m3-2-a-appendices>
</m3-quality>
```

You should provide a *manufacturer*, and *substance* or *product-name* attribute and value for every Facilities and Equipment heading element and *manufacturer*, *dosageform* and *substance or product-name*, for every Adventitious Agents Safety Evaluation heading element. There is no limit to the number of Facilities and Equipment heading and the Adventitious Agents Safety Evaluation heading elements. There is no limit to the number of *leaf* elements the Facilities and Equipment and the Adventitious Agents Safety Evaluation heading elements can contain.

### C. Heading elements and attributes for module 4

This section includes the heading and attributes elements relevant to module 4.

#### *1. Heading elements*

The module 4 heading elements are summarized in the following table. In some cases, the CTD may describe more subheadings than appear on this table. Those subheadings should be used as bookmarks within the individual document. Both the start tag and end tag for each heading element are provided. If there are one or more subheadings for the heading, the corresponding element end tag will occur on the table row below the last relevant subheading. The *leaf* element is included to show where the leaf elements should be placed. The details for the *leaf* elements

[19] Leaf element abbreviated for clarity.
[20] Leaf element abbreviated for clarity.

are not shown on this table to keep it clearer. The *leaf* elements should only occur where indicated in this table. A heading element may contain any number of *leaf* elements. If no documents are submitted for a heading, you should omit the element for that heading in the eCTD backbone file.

| Module 4 CTD Heading | eCTD Element |
|---|---|
| Module 4: Nonclinical Study Reports | <m4-nonclinical-study-reports> |
| 4.2 Study Reports | <m4-2-study-reports> |
| 4.2.1 Pharmacology | <m4-2-1-pharmacology> |
| 4.2.1.1 Primary Pharmacodynamics | <m4-2-1-1-primary-pharmacodynamics><br><leaf><br></leaf><br></m4-2-1-1-primary-pharmacodynamics> |
| 4.2.1.2 Secondary Pharmacodynamics | <m4-2-1-2-secondary-pharmacodynamics><br><leaf><br></leaf><br></m4-2-1-2-secondary-pharmacodynamics> |
| 4.2.1.3 Safety Pharmacology | <m4-2-1-3-safety-pharmacology><br><leaf><br></leaf><br></m4-2-1-3-safety-pharmacology> |
| 4.2.1.4 Pharmacodynamic Drug Interactions | <m4-2-1-4-pharmacodynamic-drug-interactions><br><leaf><br></leaf><br></m4-2-1-4-pharmacodynamic-drug-interactions> |
| End Pharmacology | </m4-2-1-pharmacology> |
| 4.2.2 Pharmacokinetics | <m4-2-2-pharmacokinetics> |
| 4.2.2.1 Analytical Methods and Validation Reports | <m4-2-2-1-analytical-methods-and-validation-reports><br><leaf><br></leaf><br></m4-2-2-1-analytical-methods-and-validation-reports> |
| 4.2.2.2 Absorption | <m4-2-2-2-absorption><br><leaf><br></leaf><br></m4-2-2-2-absorption> |
| 4.2.2.3 Distribution | <m4-2-2-3-distribution><br><leaf><br></leaf><br></m4-2-2-3-distribution> |
| 4.2.2.4 Metabolism | <m4-2-2-4-metabolism><br><leaf><br></leaf><br></m4-2-2-4-metabolism> |

| Module 4 CTD Heading | eCTD Element |
|---|---|
| 4.2.2.5 Excretion | <m4-2-2-5-excretion><br><leaf><br></leaf><br></m4-2-2-5-excretion> |
| 4.2.2.6 Pharmacokinetic Drug Interactions | <m4-2-2-6-pharmacokinetic-drug-interactions><br><leaf><br></leaf><br></m4-2-2-6-pharmacokinetic-drug-interactions> |
| 4.2.2.7 Other Pharmacokinetic Studies | <m4-2-2-7-other-pharmacokinetic-studies><br><leaf><br></leaf><br></m4-2-2-7-other-pharmacokinetic-studies> |
| End Pharmacokinetics | </m4-2-2-pharmacokinetics> |
| 4.2.3 Toxicology | <m4-2-3-toxicology> |
| 4.2.3.1 Single-Dose Toxicity | <m4-2-3-1-single-dose-toxicity><br><leaf><br></leaf><br></m4-2-3-1-single-dose-toxicity> |
| 4.2.3.2 Repeat-Dose Toxicity | <m4-2-3-2-repeat-dose-toxicity><br><leaf><br></leaf><br></m4-2-3-2-repeat-dose-toxicity> |
| 4.2.3.3 Genotoxicity | <m4-2-3-3-genotoxicity><br><leaf><br></leaf> |
| 4.2.3.3.1 In vitro | <m4-2-3-3-1-in-vitro><br><leaf><br></leaf><br></m4-2-3-3-1-in-vitro> |
| 4.2.3.3.2 In vivo | <m4-2-3-3-2-in-vivo><br><leaf><br></leaf><br></m4-2-3-3-2-in-vivo> |
| End Genotoxicity | </m4-2-3-3-genotoxicity> |
| 4.2.3.4 Carcinogenicity | <m4-2-3-4-carcinogenicity> |
| 4.2.3.4.1 Long-term studies | <m4-2-3-4-1-long-term-studies><br><leaf><br></leaf><br></m4-2-3-4-1-long-term-studies> |
| 4.2.3.4.2 Short- or medium-term studies | <m4-2-3-4-2-short-or-medium-term-studies><br><leaf><br></leaf><br></m4-2-3-4-2-short-or-medium-term-studies> |

| Module 4 CTD Heading | eCTD Element |
|---|---|
| 4.2.3.4.3 Other studies | <m4-2-3-4-3-other-studies><br><leaf><br></leaf><br></m4-2-3-4-3-other-studies> |
| End Carcinogenicity | </m4-2-3-4-carcinogenicity> |
| 4.2.3.5 Reproductive and Developmental Toxicity | <m4-2-3-5-reproductive-and-developmental-toxicity> |
| 4.2.3.5.1 Fertility and early embryonic development | <m4-2-3-5-1-fertility-and-early-embryonic-development><br><leaf><br></leaf><br></m4-2-3-5-1-fertility-and-early-embryonic-development> |
| 4.2.3.5.2 Embryofetal development | <m4-2-3-5-2-embryo-fetal-development><br><leaf><br></leaf><br></m4-2-3-5-2-embryo-fetal-development> |
| 4.2.3.5.3 Prenatal and postnatal development, including maternal function | <m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function><br><leaf><br></leaf><br></m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function> |
| 4.2.3.5.4 Studies in which the offspring | <m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated><br><leaf><br></leaf><br></m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated> |
| End Reproductive Toxicology | </m4-2-3-5-reproductive-and-developmental-toxicity> |
| 4.2.3.6. Local Tolerance | <m4-2-3-6-local-tolerance><br><leaf><br></leaf><br></m4-2-3-6-local-tolerance> |
| 4.2.3.7. Other Toxicity Studies | <m4-2-3-7-other-toxicity-studies> |
| 4.2.3.7.1 Antigenicity | <m4-2-3-7-1-antigenicity><br><leaf><br></leaf><br></m4-2-3-7-1-antigenicity> |

| Module 4 CTD Heading | eCTD Element |
|---|---|
| 4.2.3.7.2 Immunotoxicity | <m4-2-3-7-2-immunotoxicity><br><leaf><br></leaf><br></m4-2-3-7-2-immunotoxicity> |
| 4.2.3.7.3 Mechanistic studies | <m4-2-3-7-3-mechanistic-studies><br><leaf><br></leaf><br></m4-2-3-7-3-mechanistic-studies> |
| 4.2.3.7.4 Dependence | <m4-2-3-7-4-dependence><br><leaf><br></leaf><br></m4-2-3-7-4-dependence> |
| 4.2.3.7.5 Metabolites | <m4-2-3-7-5-metabolites><br><leaf><br></leaf><br></m4-2-3-7-5-metabolites> |
| 4.2.3.7.6 Impurities | <m4-2-3-7-6-impurities><br><leaf><br></leaf><br></m4-2-3-7-6-impurities> |
| 4.2.3.7.7 Other | <m4-2-3-7-7-other><br><leaf><br></leaf><br></m4-2-3-7-7-other> |
| End Other | </m4-2-3-7-other-toxicity-studies> |
| End Toxicology | </m4-2-3-toxicology> |
| End Study Reports | </m4-2-study-reports> |
| 4.3 Literature References | <m4-3-literature-references><br><leaf><br></leaf><br></m4-3-literature-references> |
| End Nonclinical | </m4-nonclinical-study-reports> |

An example of the elements used to organize the *leaf* element for the Embryo Fetal Development Toxicology heading document is provided:

<m4-nonclinical-study-reports>
<m4-2-study-reports>
<m4-2-3-toxicology>
<m4-2-3-5-reproductive-and-developmental-toxicity>
<m4-2-3-5-2-embryo-fetal-development>
<leaf></leaf>[21]
</m4-2-3-5-2-embryo-fetal-development>

[21] Leaf element abbreviated for clarity.

```
                    </m4-2-3-5-reproductive-and-developmental-toxicity>
                </m4-2-3-toxicology>
            </m4-2-study-reports>
        </m4-nonclinical-study-reports>
```

The number of *leaf* elements that the heading elements can contain is not limited.

*2. Attributes for Module 4 heading elements*

There are no attributes for Module 4 heading elements.

### D. Heading elements and attributes for module 5

This section includes the heading elements and attributes relevant to module 5.

*1. Module 5 Heading element*

The module 5 heading elements are summarized in the following table. In some cases, the CTD may describe more subheadings than appear on this table. Those subheadings should be used as bookmarks within the individual document. Both the start tag and end tag for each heading element are provided. If there are one or more subheadings for the heading, the corresponding element end tag will occur on the table row below the last relevant subheading. The *leaf* element is included to show where the leaf elements should be placed. The details for the *leaf* elements are not shown on this table to keep it clearer. The *leaf* elements should only occur where indicated in this table. A heading element may contain any number of *leaf* elements. If no documents are submitted for a heading, you should omit the element for that heading in the eCTD backbone file.

| Module 5 CTD Heading | eCTD Element |
|---|---|
| Module 5: Clinical Study Reports | <m5-clinical-study-reports> |
| 5.2 Tabular Listing Of All Clinical Studies | <m5-2-tabular-listing-of-all-clinical-studies><br><leaf><br></leaf><br></m5-2-tabular-listing-of-all-clinical-studies> |
| 5.3 Clinical Study Reports And Related Information | <m5-3-clinical-study-reports> |
| 5.3.1 Reports Of Biopharmaceutic Studies | <m5-3-1-reports-of-biopharmaceutic-studies > |
| 5.3.1.1 Bioavailability (BA) Study Reports | <m5-3-1-1-bioavailability-study-reports><br><leaf><br></leaf><br></m5-3-1-1-bioavailability-study-reports> |

| Module 5 CTD Heading | eCTD Element |
|---|---|
| 5.3.1.2 Comparative BA And Bioequivalence (BE) Study Reports | <m5-3-1-2-comparative-ba-and-bioequivalence-study-reports><br><leaf><br></leaf><br></m5-3-1-2-comparative-ba-and-bioequivalence-study-reports> |
| 5.3.1.3 In Vitro-In Vivo Correlation Study Reports | <m5-3-1-3-in-vitro-in-vivo-correlation-study-reports><br><leaf><br></leaf><br></m5-3-1-3-in-vitro-in-vivo-correlation-study-reports> |
| 5.3.1.4 Reports Of Bioanalytical And Analytical Methods For Human Studies | <m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies><br><leaf><br></leaf><br></m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies> |
| End Biopharm | </m5-3-1-reports-of-biopharmaceutic-studies> |
| 5.3.2 Reports Of Studies Pertinent To Pharmacokinetics Using Human Biomaterials | <m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials> |
| 5.3.2.1 Plasma Protein Binding Study Reports | <m5-3-2-1-plasma-protein-binding-study-reports><br><leaf><br></leaf><br></m5-3-2-1-plasma-protein-binding-study-reports> |
| 5.3.2.2 Reports Of Hepatic Metabolism And Drug Interaction Studies | <m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies><br><leaf><br></leaf><br></m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies> |
| 5.3.2.3 Reports Of Studies Using Other Human Biomaterials | <m5-3-2-3-reports-of-studies-using-other-human-biomaterials><br><leaf><br></leaf><br></m5-3-2-3-reports-of-studies-using-other-human-biomaterials> |
| End Human Biomaterials | </m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials> |
| 5.3.3 Reports Of Human Pharmacokinetic (PK) Studies | <m5-3-3-reports-of-human-pharmacokinetics-pk-studies> |

| Module 5 CTD Heading | eCTD Element |
|---|---|
| 5.3.3.1 Healthy Subject PK And Initial Tolerability Study Reports | <m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports><br><leaf><br></leaf><br></m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports> |
| 5.3.3.2 Patient PK And Initial Tolerability Study Reports | <m5-3-3-2-patient-pk-and-initial-tolerability-study-reports><br><leaf><br></leaf><br></m5-3-3-2-patient-pk-and-initial-tolerability-study-reports> |
| 5.3.3.3 Intrinsic Factor Pk Study Reports | <m5-3-3-3-intrinsic-factor-pk-study-reports><br><leaf><br></leaf><br></m5-3-3-3-intrinsic-factor-pk-study-reports> |
| 5.3.3.4 Extrinsic Factor Pk Study Reports | <m5-3-3-4-extrinsic-factor-pk-study-reports><br><leaf><br></leaf><br></m5-3-3-4-extrinsic-factor-pk-study-reports> |
| 5.3.3.5 Population Pk Study Reports | <m5-3-3-5-population-pk-study-reports><br><leaf><br></leaf><br></m5-3-3-5-population-pk-study-reports> |
| End PK | </m5-3-3-reports-of-human-pharmacokinetics-pk-studies> |
| 5.3.4 Reports Of Human Pharmacodynamic (PD) Studies | <m5-3-4-reports-of-human-pharmacodynamics-pd-studies> |
| 5.3.4.1 Healthy Subject PD And PK/PD Study Reports | <m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports><br><leaf><br></leaf><br></m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports> |
| 5.3.4.2 Patient PD And PK/PD Study Reports | <m5-3-4-2-patient-pd-and-pk-pd-study-reports><br><leaf><br></leaf><br></m5-3-4-2-patient-pd-and-pk-pd-study-reports> |
| | </m5-3-4-reports-of-human-pharmacodynamics-pd-studies> |
| 5.3.5 Reports Of Efficacy And Safety Studies | <m5-3-5-reports-of-efficacy-and-safety-studies indication="">[22] |

[22] See the description of element attributes after this table.

| Module 5 CTD Heading | eCTD Element |
|---|---|
| 5.3.5.1 Study Reports Of Controlled Clinical Studies Pertinent To The Claimed Indication | <m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication><br><leaf><br></leaf><br></m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication> |
| 5.3.5.2 Study Reports Of Uncontrolled Clinical Studies | <m5-3-5-2-study-reports-of-uncontrolled-clinical-studies><br><leaf><br></leaf><br></m5-3-5-2-study-reports-of-uncontrolled-clinical-studies> |
| 5.3.5.3 Reports Of Analyses Of Data From More Than One Study | <m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study><br><leaf><br></leaf><br></m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study> |
| 5.3.5.4 Other Study Reports | <m5-3-5-4-other-study-reports><br><leaf><br></leaf><br></m5-3-5-4-other-study-reports> |
| End Efficacy and Safety | </m5-3-5-reports-of-efficacy-and-safety-studies> |
| 5.3.6 Reports Of Postmarketing Experience | <m5-3-6-reports-of-postmarketing-experience><br><leaf><br></leaf><br></m5-3-6-reports-of-postmarketing-experience> |
| 5.3.7 Case Report Forms and Individual Patient Listings | This heading is not used. The leaf for case report forms and individual patient listings files are placed with the appropriate study report using the Study Tagging File |
| 5.4literature References | <m5-4-literature-references><br><leaf><br></leaf><br></m5-4-literature-references> |
| End Module 5 | <m5-clinical-study-reports> |

*2. Attribute for Module 5 heading elements*

The heading element for the Reports of Efficacy And Safety Studies (ES) heading, <m5-3-5-reports-of-efficacy-and-safety-studies >, has an attribute called *indication*. The purpose of the *indication* attribute is to provide abbreviation of the clinical indication being summarized under this heading. If there is more than one indication being claimed, you should create an additional ES heading element for each indication. Each ES heading element should be the same except for the unique *indication* attribute value and *leaf* content.

The indication attribute for the ES heading element begins after the element name with a space and the lowercase word *indication*. The value for the *indication* attribute is provided in a statement that begins with the equal sign and quotation mark, (="), followed by the indication attribute value and ending with a quotation mark. There should be no spaces in the indication attribute's value statement. An example of two indication attributes and their values within two ES heading elements is provided:

```
<m5-clinical-study-reports>
        <m5-3-clinical-study-reports>
                <m5-3-5-reports-of-efficacy-and-safety-studies
                                indication="pneumonia ">
                        <leaf></leaf>[23]
                </m5-3-5-reports-of-efficacy-and-safety-studies >
                <m5-3-5-reports-of-efficacy-and-safety-studies
                                indication="sepsis">
                        <leaf></leaf>[24]
                </m5-3-5-reports-of-efficacy-and-safety-studies>
        </m5-3-clinical-study-reports>
</m5-clinical-study-reports>
```

You should provide an *indication* attribute value for every ES heading element. There is no limit to the number of ES heading elements. There is no limit to the number of *leaf* elements the ES heading element can contain.

[23] Leaf element abbreviated for clarity.
[24] Leaf element abbreviated for clarity.