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

ICH M2 EWG

The eCTD Backbone File Specification for Study Tagging Files

This specification has been developed by the ICH M2 Expert Working Group and maintained by the eCTD Implementation Working Group in accordance with the ICH Process as pertains to the M2 EWG and eCTD change control as it pertains to the eCTD IWG.

The eCTD Backbone Files Specification for Study Tagging Files

Revision History

Date	Version	Summary of Changes
2003-08-13	1.0	Original version
2004-03-09	1.1	Clarifications to the original version. Constraints from original version including redundancy of information found in the index.xml file. Added duration category and values. Added "other" as route of administration value. Added new name attribute values for file tag element.
		Versions between 1.1 and 2.6 have been unpublished drafts
2004-11-17	2.6	Provides specification for both Cumulative and Accumulative Approaches for presentation of the Study Tagging Files (STF) with more detailed examples showing index and stf file relationships. Introduces ich-stf-v2-2.dtd, ich-stf-stylesheet-2-2.xsl and valid-values.xml.
2008-06-03	2.6.1	Removed Cumulative Approach to STF life cycle management and made accumulative approach the only option. Provided clarifications and corrections to text.

The Specification for Study Tagging Files (STF)

In order to help identify all of the files associated with a study, information is needed on each document including the document title, subject matter (defined by the headings under which the documents are located in the table of contents), relationship to other documents (e.g., all documents for a specific study report are related to one another), revision information (i.e., new, replace, delete, append), the location of the document and information on the sequence that included the document. The eCTD backbone files (e.g., index.xml and us-regional.xml) include many of those information items. However, the eCTD backbone files do not contain enough information on the subject matter of several documents (e.g., study report documents) to support certain regulatory uses. This additional information is provided in the STF.

An STF should be provided with the submission of any file, or group of files belonging to a study in Modules 4 and 5. STFs are required by the United States, are not required in Europe and are not allowed in Japan. The STF provides for additional heading elements and heading attributes not currently provided by the eCTD DTD. In the STF, heading elements are called *file-tags* and are included in the *doc-content* element. Heading attributes are included in the *study-identifier* element.

Refer to regional guidance for information on STF applicability.

I. START AND STOP OF THE STF

The STF is an XML instance controlled by the ICH STF Document Type Definition (DTD). The most recent DTD can be found on the ICH web site (www.ich.org). The DTD should be placed in the *dtd* subfolder of the *util* folder. The stylesheet should be in the *style* subfolder of the *util* folder. You should provide a separate STF for each study in a sequence. The name for the STF XML file should start with the term "stf-" followed by the alphanumeric code used by the sponsor to unambiguously identify the study (i.e., study-id described below) and followed by ".xml" to complete the file name.

For every submission to FDA that includes one or more files pertaining to a specific study, you should provide an STF. You should place the STF for the specific study in the module folder with the corresponding study files. You should place a *leaf* element for the STF in the appropriate Module 4 or 5 eCTD Table of Contents element in the index.xml file for that sequence. The *operation* attribute for this leaf should have a value of "new" for the first STF for that specific study in that eCTD element and "append" for any subsequent STF for that same study in that eCTD element (see "Lifecycle Management of the Study Tagging File"). Subsequent STF files should only include information on the study documents being provided or modified by the subsequent sequence. The subsequent STF should always have a *modified-file* attribute that refers to the most recently submitted STF provided for that study in that eCTD element (i.e., you should not continually “append” to the original STF). The *version* attribute for leaf elements referencing a STF should cite the version of the STF DTD used to prepare that STF (e.g.,

"STF version 2.2") to allow the development of tools that can either ignore or highlight the presence of STF XML files.

The STF root element is *ectd:study*. The STF root element contains two child elements. The prolog part of the STF XML document and the STF root element contain 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 STF
4. Indication that the file information is ended (end tag)

A sample of the root element and last line of the STF is provided below:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../../../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2" xmlns:xlink="http://www.w3.org/1999/xlink">
<!--All the elements will be provided after these elements and before the last element closing tag named </ectd:study> -->
</ectd:study>
```

Note: "../../../../" in the path expressions for STF DTD and STF stylesheet depend on the location where the STF instance is stored.

II. STUDY-IDENTIFIER ELEMENT

Information describing the study is contained in the *study-identifier* element of the STF. There are three elements contained in the *study-identifier* element: *title*, *study-id*, and *category*.

A. Title Element

The *title* element provides the full title of the study, not the title of each individual document.

B. study-id Element

The *study-id* is the internal alphanumeric code used by the sponsor to unambiguously identify this study.

C. Category Element

The *category* element provides an additional level of study organization not currently provided by the eCTD DTD. This element is only relevant for studies provided in the specific CTD sections cited below.

- 4.2.3.1 Single dose toxicity (grouped by species and route of administration)
- 4.2.3.2 Repeat dose toxicity (grouped by species, route of administration, and duration if applicable)
- 4.2.3.4.1 Long term [carcinogenicity] studies (grouped by species)
- 5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication (grouped by type of control)

Other studies do not call for any category elements. When appropriate, you should place the *category* elements at the same level as the *title* and *study-id* elements. Each category element has the attributes *name* and *info-type*. Attribute and element values should be selected from the following table. The *info-type* attribute value should be "ich" for ICH approved values or one of the regional values (e.g., "jp", "eu", "ca", "us") for region specific values.

Category Element Attributes and Values	**values for "category" element content choices**
name="species"	
info-type="ich"	mouse
info-type="ich"	rat
info-type="ich"	hamster
info-type="ich"	other-rodent
info-type="ich"	rabbit
info-type="ich"	dog
info-type="ich"	non-human-primate
info-type="ich"	other-non-rodent-mammal
info-type="ich"	non-mammals
name="route-of-admin"	
info-type="ich"	oral
info-type="ich"	intravenous
info-type="ich"	intramuscular
info-type="ich"	intraperitoneal
info-type="ich"	subcutaneous
info-type="ich"	inhalation
info-type="ich"	topical
info-type="ich"	other ([1]see footnote)
name="duration"	
info-type="us"	short
info-type="us"	medium
info-type="us"	long
name="type-of-control"	
info-type="ich"	placebo
info-type="ich"	no-treatment
info-type="ich"	dose-response-without-placebo

[1] Please consult the regional authorities before using "other".

Category Element Attributes and Values	values for "category" element content choices
info-type="ich"	active-control-without-placebo
info-type="ich"	external

The following is an example of the use of the study-identifier elements in an STF for a long term carcinogenicity study conducted in mice (species="mouse"):

```
<study-identifier>
        <title>Long term carcinogenicity study</title>
        <study-id>abc123xyz789</study-id>
        <category name="species" info-type="ich" >mouse</category>
        <category name="duration" info-type="us" >long</category>
</study-identifier>
```

III. STUDY-DOCUMENT AND DOC-CONTENT ELEMENTS

The *study-document* element contains information on the subject matter of each file that is cited as part of the documentation for a study. The *study-document* element includes the *doc-content* element. The *doc-content* element contains the *property* and *file-tag* elements.

A. Property element

The *property* element is appropriate when files might need to be grouped by an applicant provided value. Currently, this element should only be used for site identification within a study. For example, in the submission of case-report-forms, multiple forms originating from the same study site should all be grouped by the study site *property* element.

Property Element Attributes and Values	values for "property" element content choices
name="site-identifier" info-type="us"	User identified value for the site of the study.

B. File-tag element

The *file-tag* element contains the attributes *name* and *info-type*. The text value of the *file-tag* element's *name* attribute indicates the subject matter of the document. The value of the *file-tag name* attribute should be selected from the values in the table below. For the value of the *info-type* attribute, you should use "ich" if using an ICH value or one of the regional values if the value is not defined in ICH. The table below shows the specified *name* attribute values for the *file-tag* element.

name attribute values for the file-tag element (name=" ")	info-type value	Content of Document	E3 Reference
pre-clinical-study-report	ich	Pre-clinical study report ([2]see footnote)	
legacy-clinical-study-report	ich	Clinical study report submitted as one file ([2]see footnote)	
synopsis	ich	Study Report Synopsis	2
study-report-body	ich	Study Report Body	1,3 to 15
protocol-or-amendment	ich	Protocol and/or amendments	16.1.1
sample-case-report-form	ich	Sample CRF	16.1.2
iec-irb-consent-form-list	ich	IEC and IRB and Consent Form Listings	16.1.3
list-description-investigator-site	ich	Description of Investigators and Sites	16.1.4
signatures-investigators	ich	Signatures of principal or coordinating investigator(s) or sponsor's responsible officer	16.1.5
list-patients-with-batches	ich	Listing of patients receiving test drug(s) from specified batch	16.1.6
randomisation-scheme	ich	Randomisation Scheme	16.1.7
audit-certificates-report	ich	Audit Certificates or similar documentation	16.1.8
statistical-methods-interim-analysis-plan	ich	Documentation of statistical methods and interim analysis plans	16.1.9
inter-laboratory-standardisation-methods-quality-assurance	ich	Documentation of Inter-laboratory Standardization Methods and Quality Assurance or similar documentation	16.1.10
publications-based-on-study	ich	Publications Based on the Study	16.1.11
publications-referenced-in-report	ich	Publications Referenced in the Study Report	16.1.12
discontinued-patients	ich	Discontinued Patients Listing	16.2.1
protocol-deviations	ich	Protocol Deviation Listing	16.2.2

[2] Refer to *M4: Organisation Document, Granularity Annex* for instructions on how to typically construct study reports.

name attribute values for the file-tag element (name=" ")	info-type value	Content of Document	E3 Reference
patients-excluded-from-efficacy-analysis	ich	Patients Excluded from Efficacy Analysis Listing	16.2.3
demographic-data	ich	Demographic Data Listing	16.2.4
compliance-and-drug-concentration-data	ich	Compliance and/or Drug Concentration Data Listing	16.2.5
individual-efficacy-response-data	ich	Individual Efficacy Response Data Listing	16.2.6
adverse-event-listings	ich	File contains Adverse Event Listings	16.2.7
listing-individual-laboratory-measurements-by-patient	ich	Individual Laboratory Measurements Listed by Patient	16.2.8
case-report-forms	ich	CRF for an individual subject. If you are submitting in the US, you should also provide a "property" element, described below, with its "name" attribute = "site-identifier" and its value the site identification where the study was performed.	16.3
available-on-request	ich	A file listing documents available upon request for a single study. Consult regional guidance for use.	
complete-patient-list	jp	Complete patient list	
serious-adverse-event-patient-list	jp	List of patients having serious adverse events	
adverse-event-patient-list	jp	List of patients having adverse events	
abnormal-lab-values-patient-list	jp	List of patients having abnormal lab values	
data-tabulation-dataset	us	Data tabulation dataset	
data-tabulation-data-definition	us	Data definitions for data tabulation datasets	
data-listing-dataset	us	Data listing dataset	
data-listing-data-definition	us	Data definitions for data listing datasets	
analysis-dataset	us	Analysis datasets	
analysis-program	us	Program file for analysis dataset	
analysis-data-definition	us	Data definition for analysis datasets	
annotated-crf	us	Annotated CRF for datasets	
ecg	us	Annotated ECG waveform dataset	
image	us	Image files	

name attribute values for the file-tag element (name=" ")	info-type value	Content of Document	E3 Reference
subject-profiles	us	Subject profile. You should also provide a "property" element, described below, with its "name" attribute = "site-identifier" and its value the site identification where the study was performed.	
safety-report	us	IND safety report	
antibacterial	us	Antibacterial microbiology report	
special-pathogen	us	Special pathogens (e.g., fungi, parasites, mycobacteria) and immune modulator microbiology report	
antiviral	us	Antiviral microbiology report	
iss	us	Integrated analysis of safety – integrated summary of safety report	
ise	us	Integrated analysis of efficacy – integrated summary of efficacy report	
pm-description	us	Postmarketing periodic adverse event drug experience report description	

When submitting in the US using a *file-tag* element with the *name* attribute value of "subject-profile" or "case-report-forms", you should include a *property* element with the *name* attribute value "site-identifier" and *info-type* value "us". The content of the *property* element should be text that identifies the site.

IV. LIFECYCLE MANAGEMENT OF THE STUDY TAGGING FILE

When additional leaf elements are to be referenced by a particular STF, the applicant does not need to submit a complete enumeration of the categories, file-tags and leaf ID values for all the files that comprise the Study Report. The subsequent STF would contain only references to the additional leaf elements being included. The *operation* attribute value of the leaf element for the subsequent STF should be "append" and the *modified-file* attribute of that leaf element should reference the most recently submitted STF leaf element for that study in that eCTD element. The study-document information provided in this subsequent STF should only relate to what is being added in the current submission relative to the last submission for the same STF.

For example, when an STF is being submitted in a subsequent sequence to provide additional components (additions, corrections, updates, etc.) to update information in the existing STF (e.g., original STF provided in sequence 0000), the index.xml file of the subsequent sequence would contain the following leaf entry:

<m4-2-1-1-primary-pharmacodynamics>

```
  <leaf checksum-type="MD5"
    version="STF version 2.2" xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="append"
    xlink:href="m4/42-stud-rep/421-pharmacol/4211-prim-pd/stf-jm-12-345.xml"
    modified-file="../0000/index.xml#m12345"
    ID="m42111">
          <title>jm-12-345 Study Tagging File</title>
  </leaf>
</m4-2-1-1-primary-pharmacodynamics>
```

V. MODIFYING STF INFORMATION

During the lifecycle of an application, modifications to information contained in the STF might be appropriate as the result of changes to the documentation cited in the STF, changes to the categorization of information cited in the STF, or to correct errors in a previous STF.

These modifications can be grouped as:

- changes to the STF study-identifier information and
- changes to the STF study document information.

A. Changes to the STF Study Identifier Information

When an applicant determines that Study Identifier Information was incomplete or incorrect (for example, a category element value was missing or erroneous in a previously submitted STF), an STF XML file with the corrected category elements should be submitted.

For example, an applicant submits the first STF for a single-dose oral toxicity study (Study No. JM-12-345) in eCTD element 4.2.3.1 in sequence 0001. The index.xml would contain a leaf entry for this file as follows:

```
<leaf checksum-type="MD5"
    version="stf version 2.2" xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="new"
    xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/stf-jm-12-345.xml"
    ID="idm42111-0002">
          <title>Study No. JM-12-345 STF</title>
</leaf>
```

The study-identifier section of this STF contains the following information:

```
<study-identifier>
      <title>Single dose oral toxicity study in the mouse and dog</title>
      <study-id>jm-12-345</study-id>
```

```
        <category name = "species" info-type = "ich">rat</category>
        <category name = "species" info-type = "ich">dog</category>
        <category name = "route-of-admin" info-type = "ich">oral</category>
</study-identifier>
```

Clearly, the species identified by the species category tags are incorrect.

To correct this information, the applicant would submit a corrected STF in a subsequent sequence. As there is no mechanism for comparing the information contained in the study-identifier sections of the STFs submitted over time, the information contained in the study-identifier section of the most recent STF will be deemed the most current. This applies to all information contained in the study-identifier section of the STF (title, study-id and category tags).

In order to correct the study-identifier information cited above for Study JM-12-345, an additional STF would be submitted, appended to the most recent STF, containing the corrected information.

The index.xml in this subsequent sequence (0002) would contain a leaf for the new STF as follows:

```
<leaf checksum-type="MD5"
    version="stf version 2.2" xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="append"
    xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/stf-jm-12-345.xml"
    modified-file="../0001/index.xml#idm42111-0002"
    ID="a345">
            <title>Study No. JM-12-345 STF</title>
</leaf>
```

If there was no additional documentation being provided for this study (and thus the purpose of this STF is solely to correct the erroneous study-identifier information), the STF would contain the following:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
    <study-identifier>
        <title>Single dose oral toxicity study in the mouse and dog</title>
        <study-id>jm-12-345</study-id>
        <category name="species" info-type="ich">mouse</category>
        <category name="species" info-type="ich">dog</category>
        <category name="route-of-admin" info-type="ich">oral</category>
    </study-identifier>
    <study-document/>
</ectd:study>
```

Note: "../../../../" in the path expressions for STF DTD and STF stylesheet depend on the location where the STF instance is stored.
Note: The entire study-identifier block should be resubmitted containing all the category values. The <study-document/> indicates that no additional file-tags are being provided and is technically required since the *study-document* element is a technically mandatory element.

B. Changes to STF Study Document Information

During the lifecycle of an application, modifications to the Study Document Information contained in the STF might be called for as a result of changes to the documentation cited in the STF, changes to the categorization of documents cited in the STF, or to correct errors in a previous STF.

These modifications can be grouped as:

1. Adding leaf element references into an existing STF,
2. Deleting leaf elements cited in an existing STF, and
3. Correcting file-tag values for leaf elements cited by an existing STF.

1. Adding New Files to an Existing STF

To add leaf element references into an existing STF, the applicant should submit a subsequent STF referencing the leaf elements to be added to the existing STF. The index.xml for this sequence would contain a leaf element for the STF and additional leaf elements for any new files being provided in that sequence. The operation attribute value of the leaf element for the STF should be submitted with the ‘append’ operation and should modify the most recent STF for the study in that eCTD element. The operation attribute value for any additional leaf elements is dependent on the specific life cycle situation for that leaf element and would have an operation attribute value of new, append or replace.

2. Deleting Files Cited by an Existing STF

When a leaf element reference is to be deleted from an STF, a subsequent STF should not be submitted. The index.xml for this sequence should contain a leaf element with an operation attribute of "delete" referencing the leaf element to be deleted. No additional STF file would be called for since the leaf element for the file will be flagged as deleted and is thus effectively removed from the current view of the leaf elements referenced by the STF in that eCTD element.

3. Correcting File-tag Values

When an applicant determines that an incorrect file-tag value has been assigned to a study report component file in the STF, the applicant should "delete" the incorrectly tagged leaf element in the index.xml (to effectively remove the leaf element from any STF referencing it as it would no longer be current) and then reactivate the file in the backbone by including a second leaf with the operation value "new". The file does not need to be resubmitted; the reactivating xlink:href attribute points back to the original location of the file.

Then, an STF referencing this new leaf entry should be submitted with the corrected file tag value.

In the following example the applicant inadvertently tagged the synopsis file as a legacy-clinical-study-report in sequence 0000 and corrects the error in sequence 0003.

In the sequence 0000 index.xml,

```
<leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="new"
    xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/synopsis-of-jm-12-345.pdf"
    application-version="PDF 1.4"
    ID="m42111">
            <title>jm-12-345 Study Synopsis</title>
</leaf>
<leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="new"
    xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/stf-jm-12-345.xml"
    version="stf version 2.2"
    ID="m42112">
            <title>Study JM-12-345 STF</title>
</leaf>
```

In the sequence 0000 stf-jm-12-345.xml file

```
<study-document>
        <doc-content xlink:href = "../../../index.xml#m42111">
        <file-tag name = "legacy-clinical-study-report" info-type = "ich"/>
        </doc-content>
</study-document>
```

To correct the file-tag error, the following actions would be taken.

In the sequence 0003 index.xml, delete the incorrect file-tag by deleting the leaf element from the index.xml which logically deletes the legacy-clinical-study-report file-tag associated with it in the STF:

```
<leaf operation="delete"
    checksum="" checksum-type="MD5"
    modified-file="../0000/index.xml#m42111"
    ID="idm4211stf">
   <title/>
</leaf>
```

Then, resubmit a leaf element for the file with an *operation* attribute value of "new" citing the location of the file in the 0000 sequence - there is no need to send a second copy of the file:

```
<leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="new"
    xlink:href="../0000/m4/42-stud-rep/423-tox/4231-single-dose-tox/synopsis-of-jm-12-
345.pdf"
    application-version="PDF 1.4"
        <title>jm-12-345 Study Synopsis</title>
    ID="r34567">
</leaf>
```

Finally, include another STF (using the "append" operation) and associate the correct synopsis file-tag to the file.

```
<leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="append"
    xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/stf-jm-12-345.xml"
    modified-file="../0000/index.xml#m42112"
    version="stf version 2.2"    ID="r6789">
        <title>Study JM-12-345 STF</title>
</leaf>
```

In the sequence 0003 STF for JM-12-345, include the study-id tag to identify the study report being modified and include the corrected file-tag metadata:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../../../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
    <study-identifier>
        <title>Single dose oral toxicity study in the mouse and dog</title>
        <study-id>jm-12-345</study-id>
        <category name="species" info-type="ich">mouse</category>
        <category name="species" info-type="ich">dog</category>
        <category name="route-of-admin" info-type="ich">oral</category>
    </study-identifier>
    <study-document>
        <doc-content xlink:href="../../../../index.xml#r34567">
        <file-tag name="synopsis" info-type="ich"/>
        </doc-content>
    </study-document>
</ectd:study>
```

VI. STUDY DATA MANAGEMENT OPTIONS

In most situations, one study would generate one STF and the information generated from the study would reside together with the STF in the most appropriate subsection of the CTD. However, there are certain situations where one study could generate more than one STF representation. These situations might exist where:

- different analyses with distinct life-cycle management needs co-exist and should be distinguishable within the same eCTD section of the dossier
- a study generates information that should be presented in a different subsection of the CTD.

A. Distinguishing Time-Specific Analyses Within the Same Subsection of the CTD

In certain instances, the reporting of results can best be managed by maintenance of more than one STF for the same study. This situation generally arises when unique time point analyses (i.e. the latter analysis does not replace the earlier analysis) have their own life-cycle management needs, and thus are better kept as distinct reviewable units.

For example, in studies where patients continue to be followed and reported on (with or without active dosing) beyond the official, protocol-defined, efficacy and/or safety endpoints, the subsequent safety, efficacy or relapse analysis supports a different clinical purpose than the earlier analysis and thus should not replace or append the earlier analysis.

This can be illustrated through consideration of a study with protocol-defined specific time point analyses (perhaps through a Drug Safety Monitoring Board) that are required by each region to be submitted and reviewed to continue the study. Thus, in one sequence, the Applicant provides safety and efficacy data for the subset of patients with 12 weeks of exposure at that point in time. While this information is being reviewed, the Applicant submits patient data from 18 weeks of exposure as well as updates the 12-week database with the additional patients who have achieved that length of exposure. In this instance, it would not be considered appropriate to replace the 12-week data with the 18-week data. These two sets of data should be kept as distinct, reviewable units of information with their own lifecycle management needs.

B. Presenting Information from One Study in a Different Subsection of the CTD

Some studies generate data supporting more than one section of the CTD. A standard mechanism for placing this information in the appropriate CTD sections should be available. For example, a safety and/or efficacy study might also have a ‘secondary purpose’ to perform a pharmacokinetic evaluation on all or some of the patients in that study.

Filing all of this information (separate sets of analysis and supportive appendices and datasets) under just one section of the dossier is generally considered unsatisfactory, as there would be no method to associate the 'secondary' information to the proper section of the CTD. An approach might be to include the same "all-inclusive" STF in both locations to alert the reviewers that there is information contained in the STF applicable to more than one section of the CTD. However, this creates an additional burden on the reviewer in identifying which datasets, listings and appendices are relevant to the PK assessment and which are relevant to the full safety/efficacy analysis.

Thus, an applicant has the optional ability to organize these different sets of information as discrete units by creating a second STF for the same study. Information that is shared by the two analyses (e.g., protocol, Case Report Form) would be referenced by each STF while information that supports different sections of the dossier could be clearly organized and submitted in the appropriate CTD section. This is especially beneficial to applicants preparing two distinct study reports for the study (one presenting the safety/efficacy analysis on all patients and one presenting the pharmacokinetic analysis on the subset of patients who participated in that part of the study).

Before submitting information of this nature you are advised to consult regional guidance for how best to present this data.

VII. EXAMPLE SCENARIO

This section provides a series of sample sequences related to the same study.

Sequence 0000

An applicant is providing information on a placebo-controlled study in the treatment of nausea titled "Wonderdrug Study S107" performed under their in-house unique identification "S107". In sequence number 0000, the applicant provides interim study results in the form of an interim synopsis, the body of the interim study report and the protocol for the study.

The index.xml for sequence 0000 would contain four leaf entries, one for each content file and one for the STF for the study as follows:

```
<m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
  <leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="new"
    xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-contr/study-s107/synopsis.pdf"
    application-version="PDF 1.4"
    ID="a101">
```

```
            <title>S107 Study Synopsis - Interim Results</title>
  </leaf>
  <leaf checksum-type="MD5"
     xlink:type="simple"
     checksum="88e3be3f2d026b572625ab81ef5b068c" operation="new"
     xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/study-report-body.pdf"
     application-version="PDF 1.4"
     ID="a102">
            <title>S107 Study Report Body - Interim Results</title>
  </leaf>
  <leaf checksum-type="MD5"
     xlink:type="simple"
     checksum="98723f7594b5500a861509547c384e46" operation="new"
     xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/protocol.pdf"
     application-version="PDF 1.4"
     ID="a103">
            <title>S107 Study Protocol</title>
  </leaf>
  <leaf checksum-type="MD5"
     xlink:type="simple"
     checksum="25d3b246313a9dbf688a48da2295260e" operation="new"
     xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/stf-s107.xml"
     version="stf version 2.2"
     ID="a104">
            <title>Study Tagging File for S107</title>
  </leaf>
</m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-
indication>
```

The STF provided in sequence 0000 is named "stf-s107.xml" and contains the following information about the documentation being provided for study S107:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../../../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
    <study-identifier>
        <title>Wonderdrug Study S107</title>
        <study-id>S107</study-id>
        <category name="type-of-control" info-type="ich">no-treatment</category>
    </study-identifier>
    <study-document>
        <doc-content xlink:href="../../../../../index.xml#a101">
            <file-tag name="synopsis" info-type="ich"/>
        </doc-content>
```

```
        <doc-content xlink:href="../../../../../index.xml#a102">
            <file-tag name="study-report-body" info-type="ich"/>
        </doc-content>
        <doc-content xlink:href="../../../../../index.xml#a103">
            <file-tag name="protocol-or-amendment" info-type="ich"/>
        </doc-content>
    </study-document>
</ectd:study>
```

Note: "../../../../" in the path expressions for STF DTD and STF stylesheet depend on the location where the STF instance is stored.
Note: The type of control for this study was intentionally cited as "no-treatment" even though the study is a placebo-controlled study. This will be corrected in a subsequent submission (see sequence 0002).

Sequence 0001

In a subsequent submission, the sponsor wishes to provide additional documentation on Study S107. In sequence 0001, the Sponsor provides the Sample Case Report Form and a protocol amendment.

The index.xml for sequence 0001 would contain three leaf entries, one for each content file (i.e., the protocol amendment and the Sample CRF) and one for the STF which updates the previously submitted STF as shown here:

```
 <m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-
indication>
  <leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="new"
    xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/protamend01.pdf"
    application-version="PDF 1.4"
    ID="a567">
            <title>S107 Protocol Amendment No. 1</title>
  </leaf>
  <leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="88e3be3f2d026b572625ab81ef5b068c" operation="new"
    xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/samplecrf.pdf"
    application-version="PDF 1.4"
    ID="a568">
            <title>S107 Sample Case Report Form</title>
  </leaf>
  <leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="25d3b246313a9dbf688a48da2295260e" operation="append"
```

```
    xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/stf-s107.xml"
    modified-file="../0000/index.xml#a104"
    version="stf version 2.2"
    ID="a569">
            <title>Study Tagging File for S107</title>
  </leaf>
</m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-
indication>
```

The new STF is also named "stf-s107.xml" and summarizes only the new information being provided in this submission as follows:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../../../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
    <study-identifier>
        <title>Wonderdrug Study S107</title>
        <study-id>S107</study-id>
        <category name="type-of-control" info-type="ich">no-treatment</category>
    </study-identifier>
    <study-document>
        <doc-content xlink:href="../../../../../index.xml#a567">
            <file-tag name="protocol-or-amendment" info-type="ich"/>
        </doc-content>
        <doc-content xlink:href="../../../../../index.xml#a568">
            <file-tag name="sample-case-report-form" info-type="ich"/>
        </doc-content>
    </study-document>
</ectd:study>
```

Note: The type of control for this study was intentionally cited as “no-treatment” even though the study is a placebo-controlled study. This will be corrected in a subsequent submission (see sequence 0002).
Note: "../../../../" in the path expressions for STF DTD and STF stylesheet depend on the location where the STF instance is stored.

Sequence 0002

In a subsequent submission, the sponsor wishes to provide additional documentation on Study S107. In sequence 0002, the Sponsor provides the final study report and synopsis plus CRF files for two patients who died during the conduct of the study. In addition, it was finally noticed that the previous STFs had incorrectly identified the study as an uncontrolled study when, in fact, it was placebo-controlled.

The index.xml for sequence 0002 would contain five leaf entries, one for each content file (i.e., synopsis, study report and two patient CRF files) and one for the STF which would append the most recent STF as shown here:

```
<m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
  <leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="replace"
    xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-contr/study-s107/synopsis.pdf"
modified-file="../0000/index.xml#a101"
    application-version="PDF 1.4"
    ID="r345">
          <title>S107 Study Synopsis - Final</title>
  </leaf>
  <leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="88e3be3f2d026b572625ab81ef5b068c" operation="replace"
    xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-contr/study-s107/s107body.pdf"
modified-file="../0000/index.xml#a102"
    application-version="PDF 1.4"
    ID="r346">
          <title>S107 Study Report - Final</title>
  </leaf>
<leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="new"
    xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-contr/study-s107/crf/11/12.pdf"
    application-version="PDF 1.4"
    ID="r347">
          <title>CRF for Subject S107-11-12</title>
  </leaf>
  <leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="88e3be3f2d026b572625ab81ef5b068c" operation="new"
    xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-contr/study-s107/crf/162/5045.pdf"
    application-version="PDF 1.4"
    ID="r348">
          <title>CRF for Patient S107-162-5045</title>
  </leaf>
  <leaf checksum-type="MD5"
    xlink:type="simple"
    checksum="25d3b246313a9dbf688a48da2295260e" operation="append"
    xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-contr/study-s107/stf-s107.xml"
    modified-file="../0001/index.xml#a569"
```

```
    version="stf version 2.2"
    ID="r349">
            <title>Study Tagging File for S107</title>
  </leaf>
</m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-
indication>
```

The new STF is named "stf-s107.xml" and identifies the additional documentation provided for Study S107 in this submission. The information in this STF also corrects the erroneous “type-of-control” category tag to “placebo” as follows:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../../../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
    <study-identifier>
        <title>Wonderdrug Study S107</title>
        <study-id>S107</study-id>
        <category name="type-of-control" info-type="ich">placebo</category>
    </study-identifier>
    <study-document>
        <doc-content xlink:href="../../../../../index.xml#r345">
            <file-tag name="synopsis" info-type="ich"/>
        </doc-content>
        <doc-content xlink:href="../../../../../index.xml#r346">
            <file-tag name="study-report-body" info-type="ich"/>
        </doc-content>
        <doc-content xlink:href="../../../../../index.xml#r347" >
            <property name="site-identifier" info-type="us">11</property>
            <file-tag name="case-report-forms" info-type="ich"/>
        </doc-content>
        <doc-content xlink:href="../../../../../index.xml#r348" >
            <property name="site-identifier" info-type="us">162</property>
            <file-tag name="case-report-forms" info-type="ich"/>
        </doc-content>
    </study-document>
</ectd:study>
```

Note: "../../../../" in the path expressions for STF DTD and STF stylesheet depend on the location where the STF instance is stored.