BEST PRACTICE: CTD BASED ASSEMBLY

1 Contents

2 Revision History

When Ennov releases a new version of Ennov InSight, they issue Release Notes which explain the new features and updates. The Ennov Business Consulting Team reviews the Release Notes against each Best Practice to determine any impact to the document:

- Impact = Release notes-documented upgrade changes this Best Practice
- No Impact = Release notes-documented upgrade changes do not affect this Best Practice

When Release Notes impact Best Practice documentation, Ennov recommends that clients review the entire Release Notes for a full understanding of all changes associated with this Best Practice documentation.

Software Version	Release/ Revision Date	Summary of Change(s) (Refer to Release Notes for Full Description)
v7.3.1	28-Jun-2024	Update Best Practice for Ennov rebranding & for v7.3.1 – No Impact
v7.2	20-Jun-2023	Update Best Practice for v7.2 – No Impact
v7.1	13-Jan-2022	Update Best Practice for v7.1 – No Impact
v7.0	25-May-2021	Update Best Practice for v7.0 – Impact

3 CTD Based Assemblies

The recommended that you follow the best practices for CTD based submissions.

Some regional specific Forms downloaded from agency Web sites contain Adobe Dynamic XML forms and Adobe Static PDF forms that can cause issues when publishing. To avoid publishing issues, it is recommended that the Leaf for any regional Form is set to Use Native File.

3.1 Module 1 – Regional Information

It is recommended that you follow the best practices for different regions of Module 1.

- Canadian Regional Information
- EU Regional Information
- Japanese Regional Information
- US Regional Information
- AU Regional Information
- CH Regional Information
- TH Regional Information
- ZA Regional Information

3.1.1 Updating Existing CH Submissions Migrated to M1 v1.3

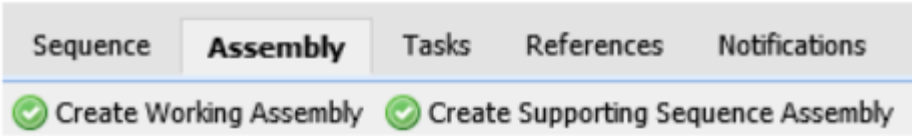
The Swiss Module 1 Specification for eCTD Version 1.3 includes changes to the XML backbone structure, and new file and folder naming conventions.

This document provides Best Practice guidance for the creation of CH submissions, according to the CH Module 1 eCTD v1.3 specification, within applications that have previously submitted submissions compliant with the previous CH Module 1 eCTD specification.

Using the Create eCTD Wizard to create a working assembly using the 1.3 DTD is not supported and can create undesired results. For any subsequent sequences, the eCTD Wizard can be used to update only manually created assemblies.

To create a new Sequence based on the CH Module 1 eCTD Specification Version 1.3:

1. Create a new Sequence within an existing Application. Go to the **Assembly** tab and click **Create Working Assembly**.



2. After the new working assembly is created and before making any modifications: go to **Publishing Settings Library**. On the **Publishing Settings** tab, remove **ch-1-2** from **the Selected XML Definitions** list and add **ch-1-3**. Click **Save**.

3. After the new XML Definition File is applied, refresh the assembly tree. Applying the ch-1-3 XML Definition File updates the assembly according to the 1.3 specification:
    a. Values in extended attributes
    b. Folder names
    c. Leaf names. Abbreviated Name, Title, and Output File attributes are updated for leafs within a working assembly
4. Check the following attributes of the leaf created as a result of any lifecycle operation, and update if necessary:
    a. Abbreviated Name
    b. Title
    c. Output File

    The Create eCTD Wizard can now be used for the Sequence. After the new ch-1-3 XML definition file is applied, the changes within the current assembly cannot be rolled back. If it is necessary to roll back the changes, the working assembly must be deleted and recreated.

3.1.2 Canadian Regional Information

The top-level folder in the Canadian Module 1 includes the necessary attributes to capture the administrative information that is included in the ca-regional.xml file.

A drop-down list is provided that includes all allowable values for the submission type; users may enter applicable text in all of the other fields. In the related sequence number field, if multiple related sequences are applicable, they should be entered separated by commas. This will result in a separate related-sequence-number element for each comma-separated value.

After the initial sequence, the operation on the ca-regional.xml file in the new sequence of the index.xml file is automatically set to new. To include a new cover letter in subsequent submissions as the first element in Module 1, users add a new leaf by right clicking on the root and choosing add leaf and will then need to move the new leaf up above the section 1.2 folder to maintain compliance with the DTD.

A sample Comprehensive TOC is included on the root of the CA Module 1 Assembly template. After this has been generated and edited as necessary, it can be moved down in the assembly so the flow of the paper volume is as desired. If this is done, the Do Not Overwrite Document option should be selected to ensure all desired entries are present. Alternatively, the Comprehensive TOC can be moved to the desired location and the TOC Range can be set to the Assembly Root.

3.1.2.1 Updating Existing Canada Submissions Migrated to the 2.2 Schema

On July 6, 2012, Health Canada announced the finalization of the Canadian Module 1 Schema Version 2.2. The new specification includes changes to the XML backbone structure and new file naming conventions.

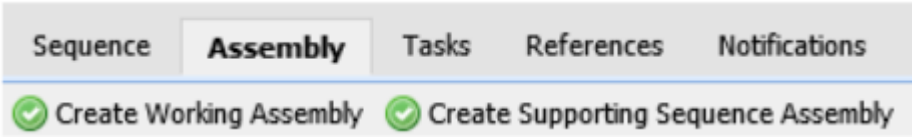
This document provides Best Practice guidance for the creation of Canadian submissions, according to the v2.2 schema, within applications that have submitted submissions that are compliant with the previous Canadian Module 1 eCTD specification. The functionality is built based on the valid scenarios provided by Health Canada: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/ectd/prep_ectd_format-eng.php

3.1.2.2 Creating New Sequences within a Cross-Specification Application CA

Using the **eCTD Wizard** to create or update a working Assembly after the switch to the 2.2 schema will not be supported and can create undesired results. After completing this procedure, it is possible to use the **eCTD Wizard** again to update the manually created assembly only.

To create a new Sequence based on the Canadian Module 1 Schema Version 2.2 specification:

1. Create a new Sequence within an existing Application. Switch to the Assembly tab and click **Create Working Assembly**.



2. After the new working assembly is created and before making any modifications, go to the **Publishing Settings Library > Publishing Settings** tab.
3. Remove ca-1-0 from the Selected XML Definitions list and add ca-2-2.
4. Click **Save**.
5. After the new XML Definition File is applied, refresh the assembly tree.

All folder names are renamed automatically according to the new 2.2 specification. The refresh also updates the Abbreviated Name, Title, and Output File attributes for all leafs within a working assembly. The new values are taken from the first leaf under the corresponding folder in CA 2.2 template and may not match the values that you have in the previously submitted sequences. If there are multiple leafs under the folder, the same attributes are applied to all of them.

Leaf attributes before ca-2-2 is applied:

Leaf attributes after ca-2-2 is applied

Note: You should check the following attributes of the leaf created as a result of any lifecycle operation, and update if necessary: Abbreviated Name, Title, and Output File.

After the new **ca-2-2 XML** definition file is applied, it is not possible to roll back the changes within the current Assembly. If it is necessary to roll back the changes, the working assembly must be deleted and recreated.

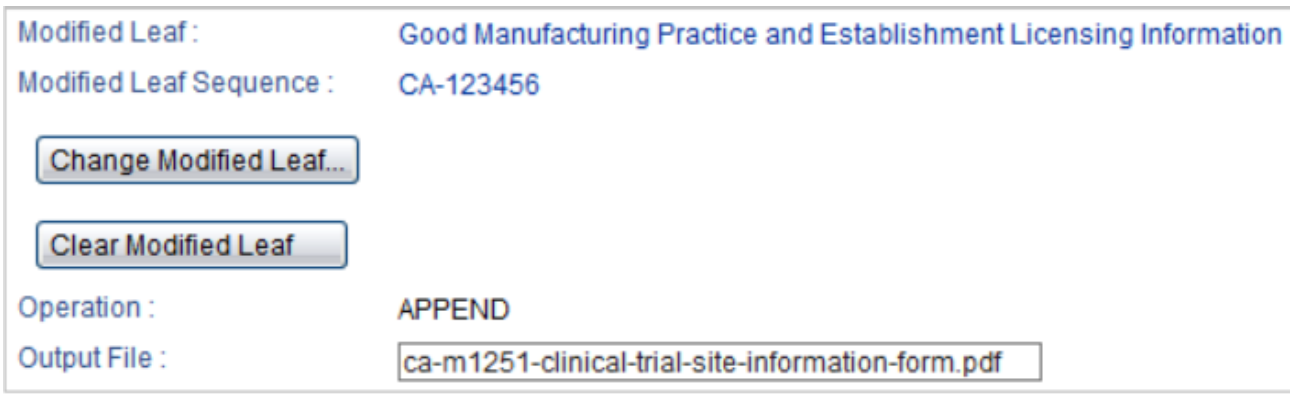
3.1.2.2.1 Append/Replace/Withdraw Operations within a Cross-Specification Application

Important: Performing a replace operation using RIM drag-and-drop functionality is not recommended, as this will cause undesirable results.

The new 2.2 specification includes changes to the structure of the XML backbone, particularly to the locations where submitted documents should be referenced. This affects the following sections in the original 1.0 template: 1.0, 1.2.4, 1.2.5, and 1.4.1.

After any lifecycle operation is invoked from a leaf that was originally submitted in one of those locations, you will be prompted to specify a new location for the append/replace/delete leaf. Choose the location and click **OK**.

The operation automatically creates any new folder and leaf that is required, with the appropriate operation. The new leaf will contain the Modified Leaf attribute set to the original leaf.



Note: Do not change the Modified Leaf attribute for the newly created leaf manually; this may cause undesired results.

3.1.2.2.2 Locations Configured for Cross-Section Append/Replace/Withdraw

By default, the following configuration is set:

Any document submitted in 1.0 section (CA 1.0) can be appended, replaced, or withdrawn within any subsection of 1.0 (CA 2.2):

1.0.1 1.0.2	1.0.3 1.0.4	1.0.5 1.0.6	1.0.7

Any document submitted in 1.2.4 section (CA 1.0) can be appended, replaced, or withdrawn within any subsection of 1.2.4 (CA 2.2):

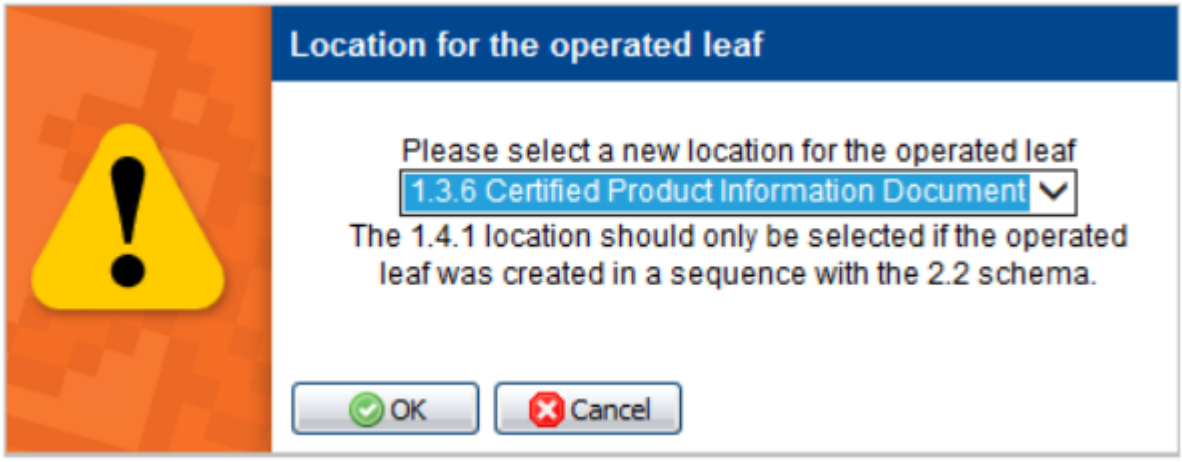
1.2.4.1 1.2.4.2

Any document submitted in 1.2.5 section (CA 1.0) can be appended, replaced, or withdrawn within any subsection of 1.2.5 (CA 2.2):

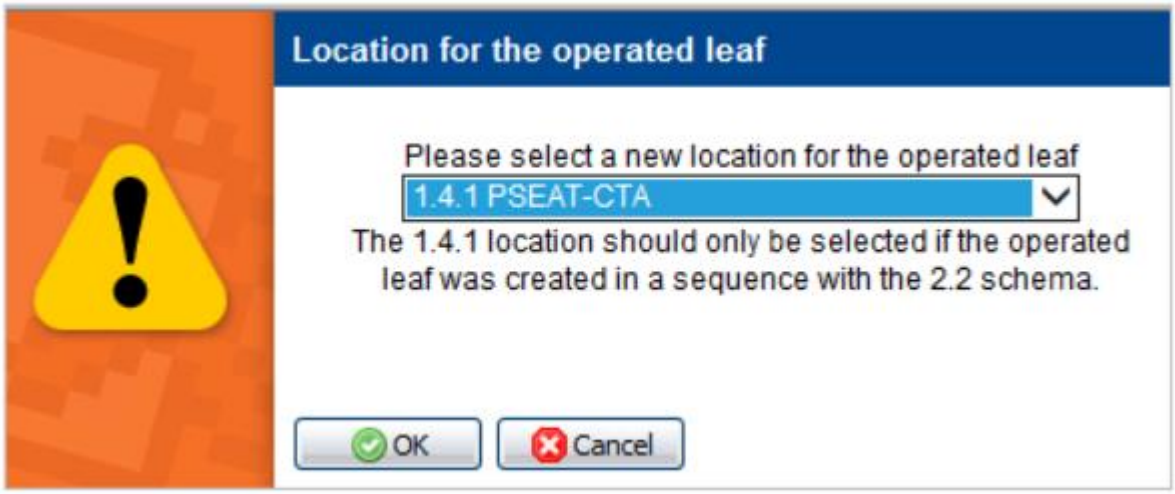
1.2.5.1 1.2.5.2	1.2.5.3 1.2.5.4	1.2.5.5 1.2.5.6	1.2.5.7

3.1.2.2.3 Append/Replace/Withdraw Operation in 1.4.1 Section

If the operation is invoked on a leaf under 1.4.1 that was submitted in a CA 1.0 submission, 1.3.6 location should be selected from the list:



If the operation is invoked on a leaf under 1.4.1 that was submitted in a CA 2.2 submission, 1.4.1 location should be chosen from the list:



3.1.2.2.4 Lifecycle Management Scenarios for Operation Attributes

- When replacing the original document, any appended document must be deleted first.
- When the original document is deleted, any appended documents must be deleted first.
- It is not a valid operation to append to a leaf that has already been appended to a new leaf. For details of other valid and invalid scenarios, please refer to the Health Canada Web site:
- http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/ectd/prep_ectd_format-eng.php#a78

3.1.2.3 Reverting of Lifecycle Operations

Reverting of lifecycle operations performed in sections 1.0, 1.2.4, 1.2.5, and 1.4.1 will remove any folders created as part of the replace/append/delete operation. Folders will not be removed if they contain other elements.

Revert of an append operation is invoked from the original leaf, which resides in the original (CA 1.0) location. Revert of the replace/delete operation is invoked from the replace/delete leaf, which resides in the new (CA 2.2) location.

3.1.2.3.1 Known Issues for Canadian Module 1 Schema Version 2.2

The following known issues are associated with the Canadian Module 1 Schema Version 2.2:

Defect	Description
22705	The same leaf can be operated in two concurrently planned working sequences, described in the following examples. In this example, two concurrently planned working sequences are based on the submitted view of 0000: **P0001** – there is a replace on the leaf in 0000 **P0002** – there is a replace on the same leaf in 0000 If P0001 is submitted, and then P0002 is added, the replace operation in P0002 should be updated automatically to point to the replace leaf in P0001. This replace operation will not occur if there are cross-section lifecycle operations in the sequences. In this example, there are two concurrently planned working sequences based on the submitted view of 0000: **P0001** – there is a delete on the leaf in 0000 **P0002** – there is a replace on the same leaf in 0000 If P0001 is submitted, and then an attempt is done to add P0002 to the lifecycle, an error message should appear indicating that leaf has been removed from the submitted view in the other sequence and the operation cannot be performed on it. This will not happen if there are cross-section lifecycle operations.
22704	Lifecycle History Query will not show the complete lifecycle history for leafs created with a lifecycle operation that includes leafs moved to a different section. The report does not track leaf migration from the old section to the new section. As a result, only operations at the new section are visible.

3.1.2.4 EU Regional Information: Procedure Types

Ennov InSight includes EU Module 1 templates to address each combination of available specifications, v1.0, v1.1, v1.2.1, v 1.3, v 1.4, v2.0, v3.0, v3.0.1 and procedure types: Centralised (CP), Mutual Recognition/Decentralised (MRP-DCP), and National (NP).

Your administrator can configure the server to set the Wizard to use a specific version and procedure type by default. However, when executing the Wizard, users may choose the applicable template for their application from the drop-down list.

The older specification templates may be removed from the drop-down list by the Administrator by modifying the configuration file on the server.

The EU Module 1 assembly structure is designed to allow users to enter envelope information for multiple countries by adding a folder under the EU Envelope information leaf for each country for which envelope information is provided. Whenever country-specific information is provided in a sequence, a corresponding envelope for that country should always be included.

The samples included in the templates are driven by the procedure type included in the template name.

- The CP template includes only EMA structures for the country-specific sections; the SPC Labelling section is organized by labeling type and then language.
- The MRP/DCP template includes all country and language combinations as well as the 'common' option for the country-specific sections; the SPC Labeling section is organized by country, language, and then labeling type.

- The NP template is similar to the MRP/DCP template by including all country and language combinations, but does not include the 'common' option in the country-specific sections.

After indicating the Procedure type of the application, the Create eCTD Wizard prompts you to select the appropriate template and applicable countries for the sequence. When displaying the structure for you to select applicable sections for the assembly, it filters the template so that only associated countries are available for selection.

The resulting association of the sequence to the countries in Ennov InSight is also controlled by this association. When creating a CP application, it will be organized only under the European Union, as opposed to displaying under all EU countries as it did in previous releases of Ennov InSight. For MRP/DCP applications, after the first country's envelope information is populated, the common information cascades to all subsequent countries, eliminating the need for redundant data entry and the potential inconsistencies across countries. The Agency information can be managed in Data Administration so that the Wizard will pre-populate each country's Agency information automatically.
When entering the Application Number information, it should be noted that while multiple application numbers may be associated with a single application, only the number(s) applicable for the specific regulatory activity should be included in a single sequence.

Note: When an initial sequence assembly is created using Create Assembly from a Template, Assembly, or View option, or if parts of an existing assembly that includes elements with extended attributes defined, are imported into an assembly the extended attributes from the source assembly will be copied to the target assembly. It is recommended that you review and update the copied information carefully to match the values of the target assembly. The attributes such as application number, sequence number, submission type, and UUID must be updated to represent the target submission.

3.1.2.5 EU Regional Information: Specification-specific Information

In order to be compliant with the DTD, every sequence should always include a cover letter. You will need to add a new cover letter each time, using one of the following methods:

- Select the 1.0 (Country) Cover Letter folder and add a new leaf under it, then assign content.
- Select a Cover Letter leaf from a previous sequence, right-click and choose Duplicate Leaf.
- Drag-and-drop the new sequence's cover letter document from the DMS Browser directly onto the 1.0 (Country) Cover Letter folder, which will automatically create the new leaf and assign the content.

Many of the folders in the assembly templates include comments that provide helpful hints in completing the sections. These more complex sections include:

3.1.2.5.1 All Specification Versions

- Section 1.2 for the Application form may include the electronic XML application form or the traditional PDF version. Samples of both types are included in the assembly structure with extended folder types applied. When the eAF is provided, the eu-forms XML Definition file should be active and the appropriate extended type must be used to ensure the eAF supportive files are copied to the appropriate location.
- Section 1.6 in all versions of the specification is restricted so that only section 1.6.1 or 1.6.2 may be included. The unused section must be deleted to produce compliant XML.

- The Additional Data Section, generally, should not be used in the Centralised Procedure except in cases where a change has been made in the regulations or Notice to Applicants to introduce a requirement for new information for which there is not yet a section in the current specification.

3.1.2.5.2 Version 1.2.1 and Beyond

- Section 1.3.1 may include both traditional PDF labeling and PIM labeling in the v1.2.1 specification and beyond to allow for lifecycle transition from PDF to PIM formats. When transitioning from PDF labeling to PIM, the applicant is instructed to perform a delete on the leaf elements included under the SPC Labeling section and add the PIM leaf as new. The file name of the PIM leaf should be updated to reflect the current sequence information prior to publishing.
- In the Responses to Questions Section, the use of node-extensions is recommended to organise the responses by regulatory activity and technical sections. These may be created in Ennov InSight by creating new folders under the appropriate country's Responses folder and using the Change Type function to set the folder type to Node Extension.

3.1.2.5.3 Version 1.1

- Section 1.3.1 is limited to include either traditional PDF labeling or PIM labeling in the v1.1 specification. A sample of each type of structure is included in the assembly template, but whichever is not being used must be deleted. There are extended types applied to these folders to ensure appropriate XML and output folder creation.
- Section 1.5 in the v1.1 template includes 5 subfolders to reflect the latest Notice to Applications, but sections 1.5.3-5 are included as node-extensions as the v1.1 spec restricted this section to have only 1.5.1 or 1.5.2 or a node-extension. This structure was created to reflect the comments in the v1.2 specification Withdrawal notice.

3.1.2.5.4 Version 1.0

- Section 1.5 when using the v1.0 specification has restrictions in them whereby they should only include one of their potential two subsections. The EU v1.0 template includes both subsections in each section; users should delete the non-applicable subsection prior to completing the assembly in order to produce compliant XML.

When providing a Non-electronic eCTD (NeeS) or paper to accompany the eCTD, a sample comprehensive TOC is included on the root of the Module 1 template. The user may choose to update this template and move the TOC element between the 1.0 and 1.2 sections and set the range of the TOC at the root using the Set Range functionality.

3.1.3 Updating Existing EU Submissions Migrated to v2.0

In February 2013, EMA announced the release of the EU Module 1 eCTD Specification Version 2.0. The specification includes changes to the XML backbone structure, new file naming conventions, and enables marketing authorization applications in Croatia.

This document provides Best Practice guidance for the creation of EU submissions, according to the EU Module 1 eCTD v2.0 specification, within applications that have previously submitted submissions compliant with the previous EU Module 1 eCTD specification.

3.1.3.1 Updating MRP/DCP Applications to include Croatia

Change the Application to add Croatia as a Concerned Member State.

1. Navigate to the **Application Attributes** page of the application to which the submission belongs.
2. Choose the **Countries** tab and click the **Add Application Country** icon.
3. On the opened **Add Application Countries** page, move Croatia from the list of **Available Concerned Member States** to the list **of Selected Concerned Member States**.
4. Click **Save**.

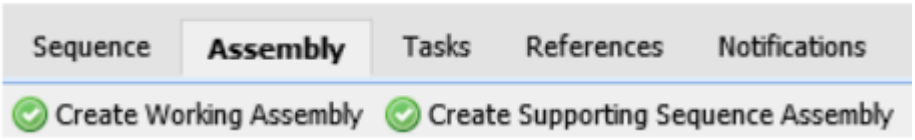
For all Subsequent Events and Sequences, Croatia will be available to select as an Event Country and as a Concerned Member State.

3.1.3.2 Creating New Sequences within a Cross-Specification Application EU v2.0

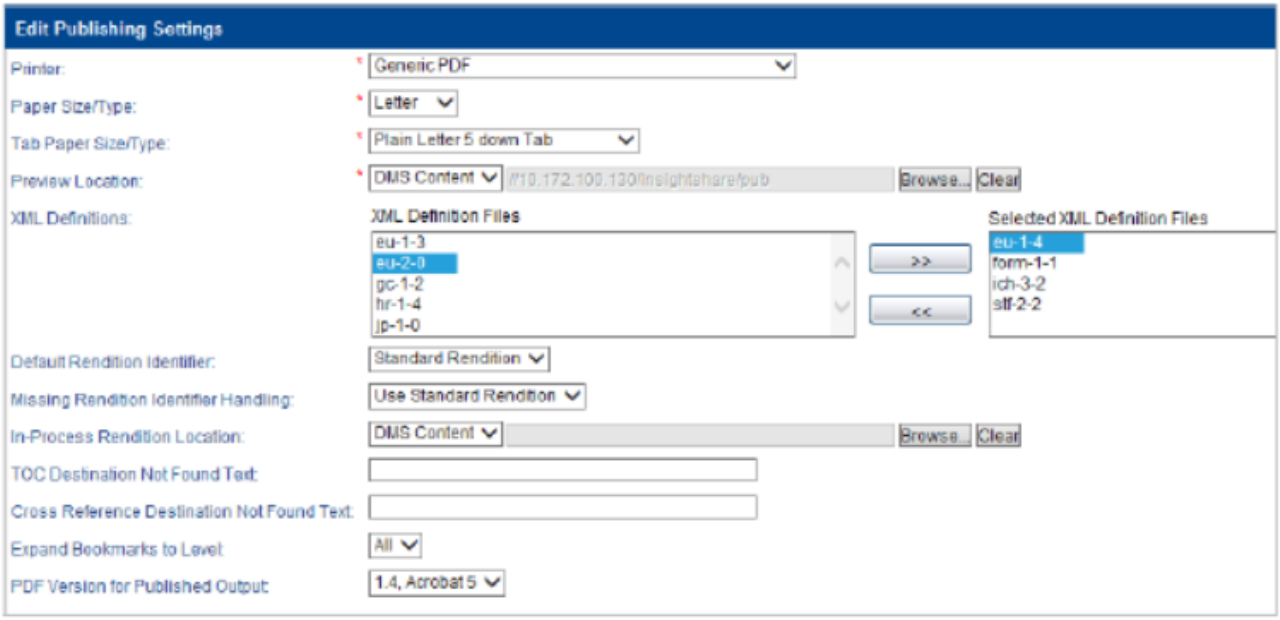
Using the **eCTD Wizard** to create or update a working assembly after the switch to the 2.0 DTD is not supported and can create undesired results. For any subsequent sequences, the **eCTD Wizard** can be used to update manually created assembly only.

To create a new Sequence based on the EU Module 1 eCTD Specification Version 2.0:

1. Create a new Sequence within an existing Application. Switch to the **Assembly** tab and click **Create Working Assembly.**



2. After the new working assembly is created and before making any modifications: go to **Publishing Settings**, and on the **XML Definitions** tab remove eu-1-4 from the Selected XML Definitions list and add eu-2-0.
3. Click **Apply**.



4. After the new XML Definition File is applied, refresh the assembly tree. Applying the eu-2-0 XML Definition File updates the assembly according to the new 2.0 specification:
    a. Values in extended attributes
    b. Folder names
    c. Leaf names, Abbreviated Name, Title, and Output File attributes are updated for leafs within a working assembly.
5. Select the following attributes of the leaf created as a result of any lifecycle operation, and update if necessary: **Abbreviated Name, Title,** and **Output File**. It is now possible to use the **Create eCTD Wizard** for this Sequence.
6. Run the **Create eCTD wizard** to add Croatian country-specific nodes to the existing assembly.
    a. Navigate to the assembly that needs to be updated and choose **Wizards > Create eCTD**.
    b. On the Choose Region page, make sure that Croatia is selected. Enter the necessary information for the Croatia envelope.
    c. On the **Select Attributes** page, enter the envelope attributes for Croatia and proceed with the wizard.
    d. On the **Select Sections** page, choose the sections you need to add and finish the wizard.

After the new eu-2-0 XML definition file is applied, the changes within the current assembly cannot be rolled back. If it is necessary to roll back the changes, the working assembly must be deleted and recreated.

3.1.3.3 Removal of PIM Labelling (1.3.1)

The new 2.0 specification includes changes to the structure of the XML backbone.
The m1-3-1-pim element, which corresponded to the 1.3.1 PIM Labeling section in the EU v1.4.1 template, has been removed. At the time of release the EMA has not responded to requests to describe how the removal of 1.3.1 PIM Labeling should be done. As a precaution, no operations should be performed on this leaf as this will cause invalid XML.

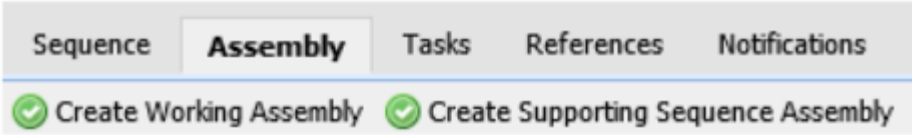
3.1.4 Updating Existing EU Submissions Migrated to v3.0

This topic describes Best Practice guidance for the creation of EU submissions, according to the EU Module 1 eCTD v3.0 specification, within applications that have previously submitted submissions compliant with the previous EU Module 1 eCTD specification.

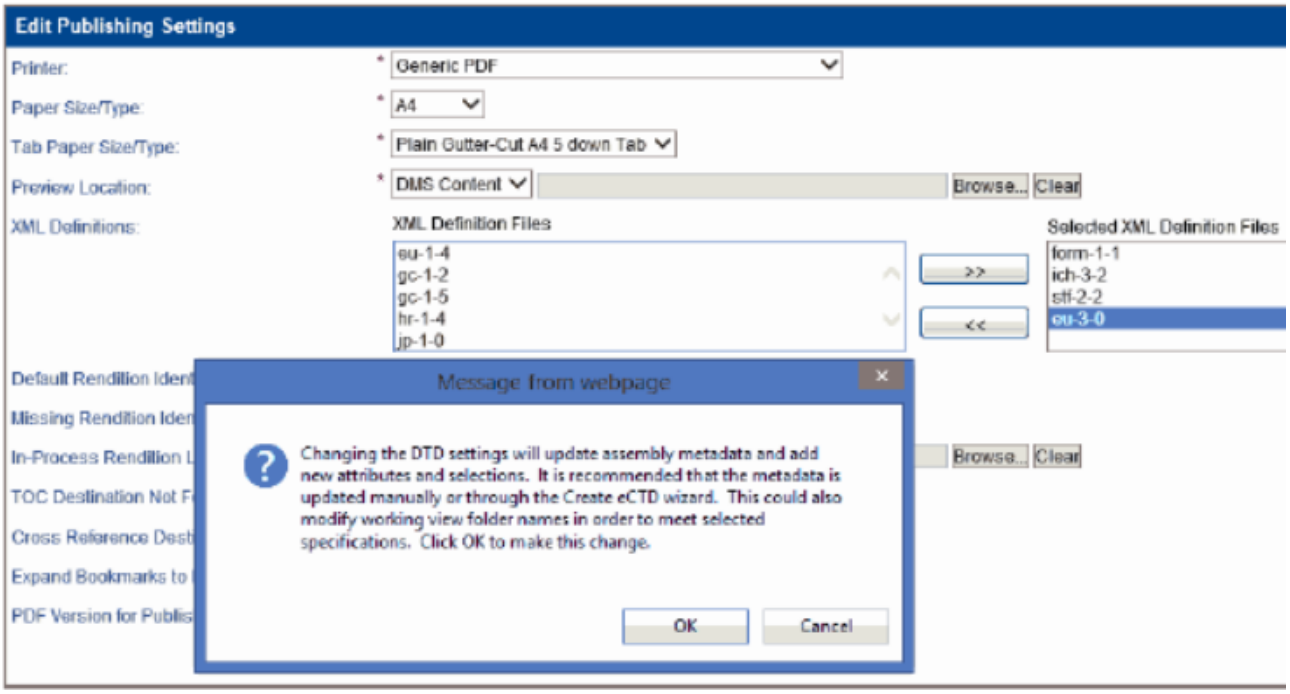
Using the **eCTD Wizard** to create or to update a working assembly after the switch to the 3.0 DTD is not supported and can create undesired results. For any subsequent sequences, the eCTD Wizard can be used to update manually created assembly only.

To create a new Sequence based on the EU Module 1 eCTD Specification Version 3.0:

- Create a new Sequence within an existing Application.
- Switch to the **Assembly** tab and click **Create Working Assembly**.



- After the new working assembly is created and before making any modifications: go to **Publishing Settings Library** (click Edit Publishing Settings Library), and on the **XML Definitions** tab remove eu-2-0 from the **Selected XML Definitions** list and add eu-3-0.



- Click **Apply**.
- After the new XML Definition File is applied, refresh the assembly tree. Applying the eu-3-0 XML Definition File updates the assembly according to the new 3.0 specification:
    a. Values in extended attributes

b. Folder names
c. Leaf names, Abbreviated Name, Title, and Output File attributes are updated for leafs within a working assembly

Note: Folder Names and Leaf attributes are updated for the applications that have previously submitted submissions compliant with EU Module 1 eCTD Specification v1.4.

- Check the following attributes of the leaf created as a result of any lifecycle operation, and update is necessary:
  a. Abbreviation Name
  b. Title
  c. Output File

It is now possible to use the **Create eCTD Wizard** for this Sequence. After the new eu-3-0 XML definition file is applied, the changes within the current assembly cannot be rolled back. If it is necessary to roll back the changes, the working assembly must be deleted and recreated.

3.1.5 Publishing of Submissions for Certificates of Suitability (CEPs) in Ennov InSight

This topic describes Best Practice guidance for the creation of Certificates of Suitability (CEPs) submissions to EDQM, according to the EU Module 1 eCTD v3.0.1 Specification.

The document includes steps for:

- Application Creation
- Sequence Creation
- eCTD Assembly Creation
- Assembly Configuration

A CEP submission is submitted to the EDQM as a single authority submission. The Application Procedure Type should be EU-National so that Ennov InSight will treat the application as a single authority Application (the Procedure Type in the Submission XML will be Centralised, per guidance, in the Assembly Attributes).

Create an Application within Ennov InSight that has the following configuration:

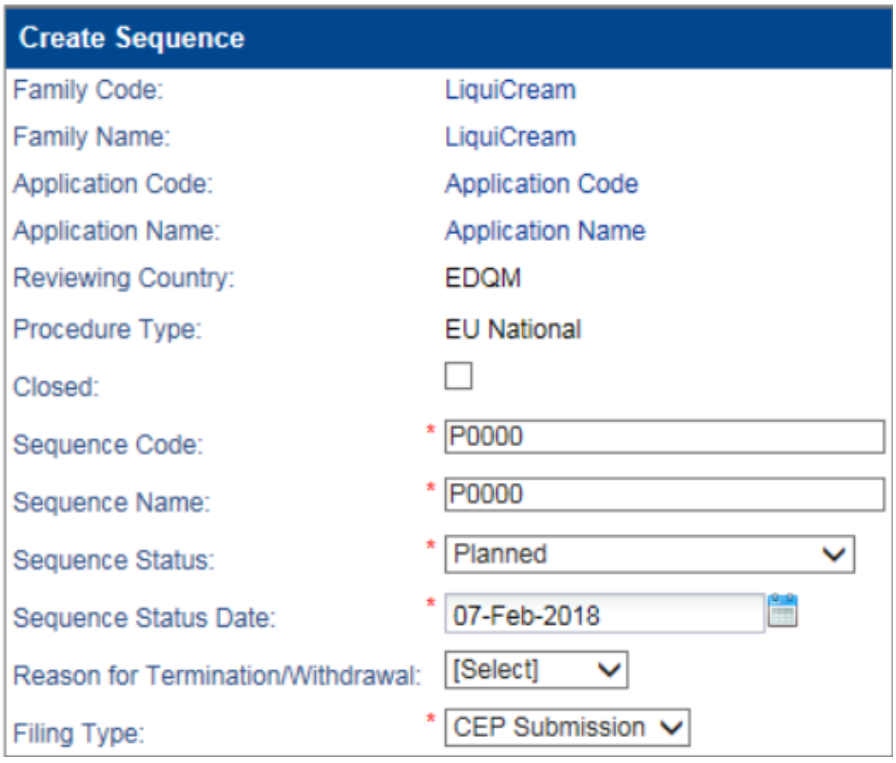
Application Attributes

Add entity to Favorites | Product Family: LiquiCream » Application: Application Na

Family Code:	LiquiCream
Family Name:	LiquiCream
Reviewing Country:	EDQM
Region(s):	Regulatory Region - European Union
UUID:	87ba854a-e215-4dcd-a0d4-b9e5754578e4
Applicant ID:	
Internal Code:	
Application Code:	Application Code
Application Name:	Application Name
Application Type:	Marketing Authorisation Application
Procedure Type:	EU - National

3.1.5.1 Sequence Creation

Create a Sequence with the following attributes:



Create Sequence

Family Code:	LiquiCream
Family Name:	LiquiCream
Application Code:	Application Code
Application Name:	Application Name
Reviewing Country:	EDQM
Procedure Type:	EU National
Closed:	☐
* Sequence Code:	P0000
* Sequence Name:	P0000
* Sequence Status:	Planned
* Sequence Status Date:	07-Feb-2018
Reason for Termination/Withdrawal:	[Select]
* Filing Type:	CEP Submission

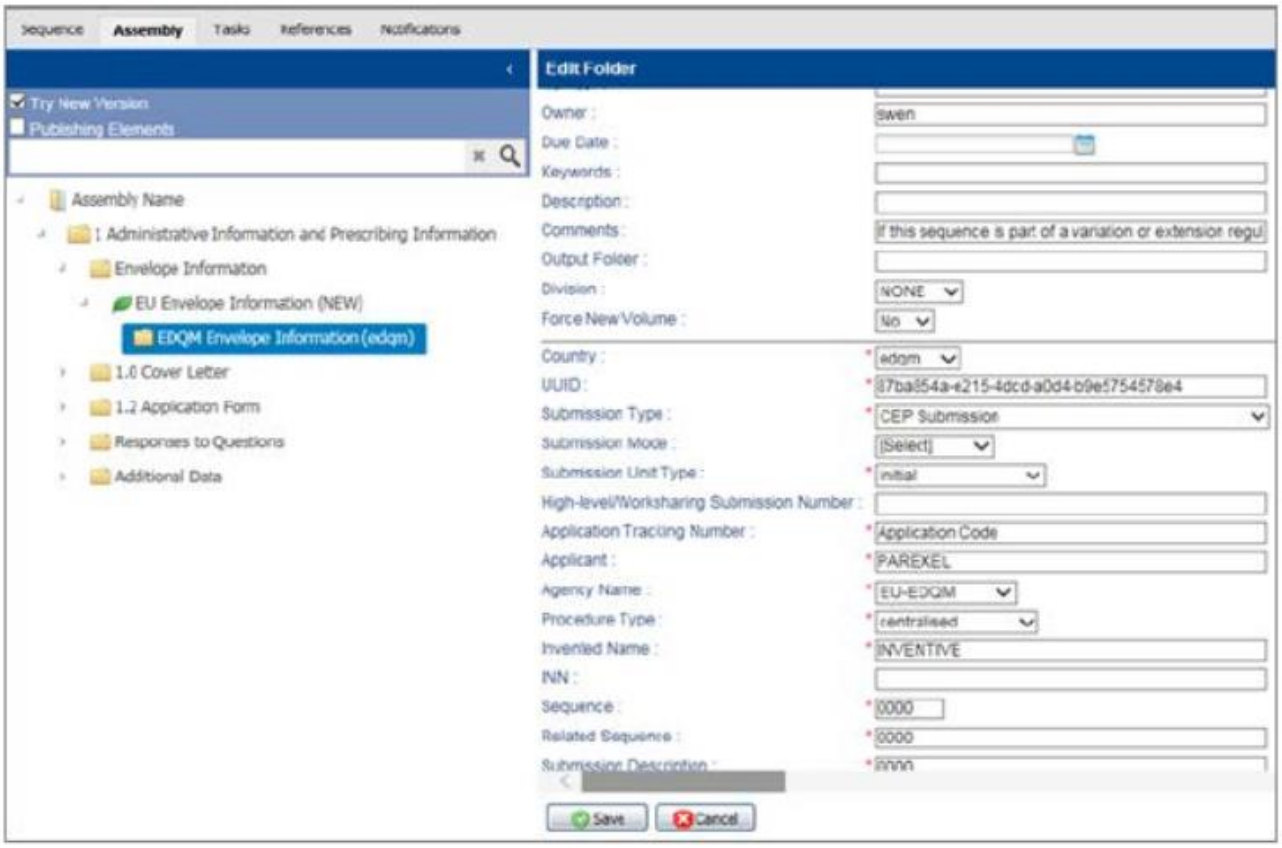
3.1.5.2 eCTD Assembly Creation

Create an eCTD Assembly. The Assembly should be created from an EU eCTD Module 1 v3.0.1 - National template (or a template created from an EU eCTD Module 1 v3.0.1 - National template). If using the Create eCTD Wizard, select the EU 3.0.1 National template as shown in this image:

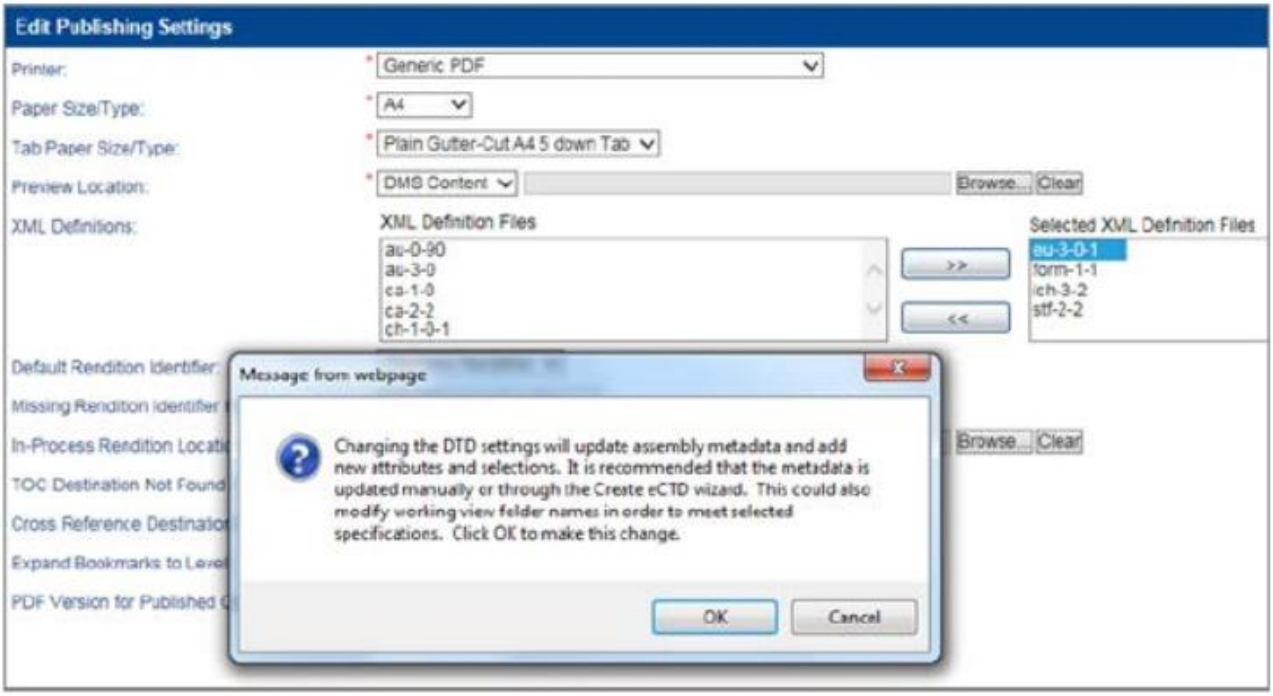
Note: CEP submissions are built using the EU National assembly template rather than the EU Centralised assembly template because they are single-authority Applications. The procedure type will be changed to Centralised in the Assembly Attributes.

3.1.5.3 Assembly Configuration

The assembly metadata can be changed by editing the information in the EDQM Envelope Information folder. The Procedure Type should be changed to Centralised in adherence to EDQM Guidance for electronic submission for Certificates of Suitability (CEP) applications as shown in this image:



The publishing settings XML Definitions should be set as follows:



3.1.6 Updating Envelope Information for EU Submissions

When an initial sequence assembly is created using Create Assembly from a Template, Assembly, or View option, or if parts of an existing assembly that includes envelope information with extended attributes defined, are imported into an assembly the extended attributes from the source will be copied to the target assembly.

It is recommended that you review and update the copied envelope information carefully to match the values of the target assembly. The attributes such as application number, sequence number, submission type, and UUID must be updated to represent the target submission.

3.1.7 Japanese Regional Information

The top-level Module 1 folder in the Japanese assembly includes the necessary attributes to capture the administrative information that is included in the jp-regional-index.xml file. If multiple brand names and/or generic names are applicable they should be entered as comma-separated values. This will result in separate property elements in the XML for each comma-separated value, with their appropriate "sequencenumber" information.

To address the cumulative requirements of Japanese eCTDs, users can set the operation on the Module 1 folder in Japanese assemblies to indicate if the operation is new, as in the case of the initial submission, or replace as in the case of subsequent submissions. The modified file value is automatically calculated and included in the output.

Each leaf in Module 1 of the Japanese assembly template has the type of Japanese Leaf to capture the sequence of the leaf within Module 1 subsections when there is more than one in a section. The value of the sequence attribute on these Japanese leafs is used to complete the "sequencenumber" property for each doc-content element within the content-block subsections. If there is only one leaf in a given subsection, this attribute should be left blank. If adding a leaf with operation="new" at any point, remember to set the type to "Japanese Leaf" to ensure the "sequencenumber" value can be captured. If performing lifecycle operations on existing leaf elements, this is not necessary as the leaf type information is carried forward when performing lifecycle operations.

When providing attribute values for sections 3.2.S, 3.2.P, and 5.3.5, by default, these values are used in constructing the output path for the files in this section (m3/32-body-data/32s-drug-sub/sub-1-mfg-1, etc). These extended attributes may be populated using Japanese characters, but the Output folder should then also be populated with "legal" characters as Japanese characters are not to be used in the output paths. So, if Japanese characters are used for the extended attributes of the 3.2.S Drug Substance, 3.2.P Drug Product, and/or 5.3.5 Clinical Indication folders, the output folders should be populated as follows to override the default inclusion of the Japanese characters in the paths:

- 32s-drug-sub/sub-1-mfg-1 – where the italicized information is the substance and manufacturer names using lower case a-z, numbers and/or hyphens only
- 32p-drug-prod/prod-1-form – where the italicized information is the product and dosage form information using lower case a-z, numbers and/or hyphens only
- 535-rep-effic-safety-stud/indication – where the italicized information is the indication using lower case a-z, numbers, and/or hyphens only

The Publishing Readiness Query and the Publishing Log will report any errors if these changes are not made, so there are safeguards in place to prevent the use of invalid characters in paths, and where possible, they will be replaced, such as in the case of upper case letters or spaces, but Japanese characters cannot simply be replaced so user action is necessary.

When providing paper to accompany the eCTD, a sample comprehensive TOC is included on the root of the Module 1 template. After this TOC is generated, it can be moved to the desired location in the assembly so it flows correctly in the paper volume. If this is done, the Do Not Overwrite Document option should be selected to ensure all desired entries are present.

3.1.8 US Regional Information

3.1.8.1 FDA Forms

FDA Forms downloaded from the FDA website contain Adobe Dynamic XML forms and Adobe Static PDF forms. These forms can cause issues when publishing. To avoid publishing issues, it is recommended that the Leaf for any FDA Form is set to Use Native File.

3.1.8.2 Administrative Information

The top-level folder in the US Module 1 assembly includes the necessary attributes to capture the administrative information included in the us-regional.xml file. Drop-down lists are provided for application type and submission type that contain the allowable values according to the specifications. Various product names may be provided for the established, proprietary, chemical and/or code names of the product. A drop-down list is provided to control the type of product name provided in the corresponding text field. To provide multiple product names, click the Add button, select the applicable type, and enter the product name. If you accidentally add a product row, leave the name field blank. After saving the attributes, the additional row will be removed.

3.1.8.3 Structured Product Labeling (SPL)

A folder for SPL content is included in each of the appropriate subsections of section 14. SPL files (such as XMLs, GIFs, JPGs) can be dragged to the SPL folder and a separate leaf for each is automatically created. Depending on the file type, the **Use Native File=Yes** flag may automatically be set for those file types that are typically provided only in their native format. Users should verify the setting for **Use Native File** is appropriate for each auto-created leaf. This information is reportable in the Publishing Readiness Report or on a leaf-by-leaf basis.

3.1.8.4 Lifecycle

After the initial sequence, the operation on the us-regional.xml file in the new sequence of the index.xml file is automatically set to New. The operation on forms in section 1.1 and the cover letter is generally new unless one was previously submitted in error. To add these new leafs, select the applicable folder, right-click, and select New Leaf to add a new leaf for the current sequence.

3.1.8.5 FDA Updates

As part of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85), enacted on September 27, 2007, the FDA announced the requirement for a new certification form (Form FDA

3674). An updated US Module 1 DTD was not issued to accompany this form, but this will be included as part of the US Module 1 DTD v3.3. In the interim, FDA has indicated to that the forms should be included as its own leaf under section 1.2 Cover Letter with a leaf title FDA Form 3674. The assembly template was not updated to include this leaf, because it is an interim placement until such time as the new DTD and specification are accepted. However, Ennov InSight will not prevent creation of this leaf in this section.

The FDA also announced the use of prefixes on the top-level application folder to identify the submission types. This has affected any cross-application references to previously submitted content. Ennov InSight does not prohibit the use of the prefixes in the initial Application code, so that your submission can be submitted using the prefix. However, recommends consulting with FDA before including it to ensure no changes to the practice have taken place because this is not documented in formal guidance. If you choose not to use the prefixes on your top-level folder but need to make cross-application references to content, Ennov InSight provides the option when creating a reference leaf to use the application prefix to ensure correct navigation.

When providing paper to accompany the eCTD, a sample comprehensive Table of Contents (TOC) is included on the root of the Module 1 template. After this TOC is generated, it can be moved to the preferred location in the assembly to flow correctly in the paper volume. If the TOC is moved, select the Do Not Overwrite Document option to ensure that all entries are included.

3.1.9 Updating Existing US Submissions Migrated to v2.3 (DTD v3.3)

This document provides Best Practice guidance for the creation of US submissions, according to the US Module 1 eCTD v2.3 specification (DTD v3.3), within applications that have previous submissions compliant with the US Module 2.01 eCTD specification.

3.1.9.1 Data Administration Updates

To support the US Module 1 updates, new fields are added to the Assembly DTD/Schema Types values. These new fields must be configured correctly in Ennov InSight Data Administration before the required metadata values can be added in Ennov InSight.

Where the code is “us-2-01”, or “us-3-3”:

- Set the Region to: United States
- Set the Countries to: United States

3.1.9.2 Creating Multiple 1.15.2.1 Material Sections

US Module 1 eCTD v2.3 specification (DTD v3.3) enables the creation of multiple 1.15.2.1 sections. Each section is defined by a unique combination of the following attributes: Promotional Material Type, Promotional Material ID, and Issue Date.

Multiple 1.15.2.1 Material sections within Ennov InSight can be created using the Create eCTD wizard or by performing a special operation on a leaf in section 1.15 from the US 2.01 submission.

3.1.9.3 Lifecycle Management Scenarios for Operation Attributes

- When replacing the original document, any appended document must be deleted first.
- When the original document is deleted, any appended documents must be deleted first.

- It is not a valid operation to append to a leaf that has already been appended to a new leaf.

3.1.9.4 Reverting Lifecycle Operations

Reverting lifecycle operations performed in sections 1.2, 1.7.1, 1.7.3, 1.9.5, 1.11.2, 1.11.3, 1.11.4, 1.12.4, 1.13.9, 1.13.12, 1.13.13, 1.15, and 1.16 will remove any folders created as part of the replace/append/delete operation. Folders will not be removed if they contain other elements.

Revert of an append operation is invoked from the original leaf, which resides in the original (US 2.01) location. Revert of the replace/delete operation is invoked from the replace/delete leaf, which resides in the new (US 3.3) location.

3.1.10 AU Regional Information

3.1.11 Updating an AU Submission to Migrate to v3.1

For an application that has a submission that was compliant with an AU Module 1 eCTD specification version before v3.1, create an AU submission that is compliant with the v3.1 specification.

The AU eCTD Module 1 Specification Version 3.1 introduces structural changes to AU eCTD Module 1 Specification Version 3.0.

3.1.11.1 1 Administration Information and Prescribing Information: New Sections

The following new sections are added to the 1.3 Medicine information and labeling folder:

- Product information – approved
- Consumer medicine information – approved

3.1.11.2 1 Administration Information and Prescribing Information: Updated Sections

The following sections are updated in the 1.3 Medicine information and labeling folder:

AU eCTD Module 1 Specification Version 3.0 Section Name	**AU eCTD Module 1 Specification Version 3.1 Section Name**
1.3.1.3 Package Insert	1.3.1.4 Package Insert
1.3.3 Label mock-ups and specimens section	The section is divided as follows: ▪ 1.3.3.1 Label mock-ups and specimens – clean ▪ 1.3.3.2 Label mock-ups and specimens - annotated ▪ 1.3.3.3 Label mock-ups and specimens - approved

The following section is updated in the 1.5 Specific requirements for different types of applications folder:

AU eCTD Module 1 Specification Version 3.0 Section Name	**AU eCTD Module 1 Specification Version 3.1 Section Name**
1.5.2 Orphan designation	1.5.2 Designation applications - supporting documents

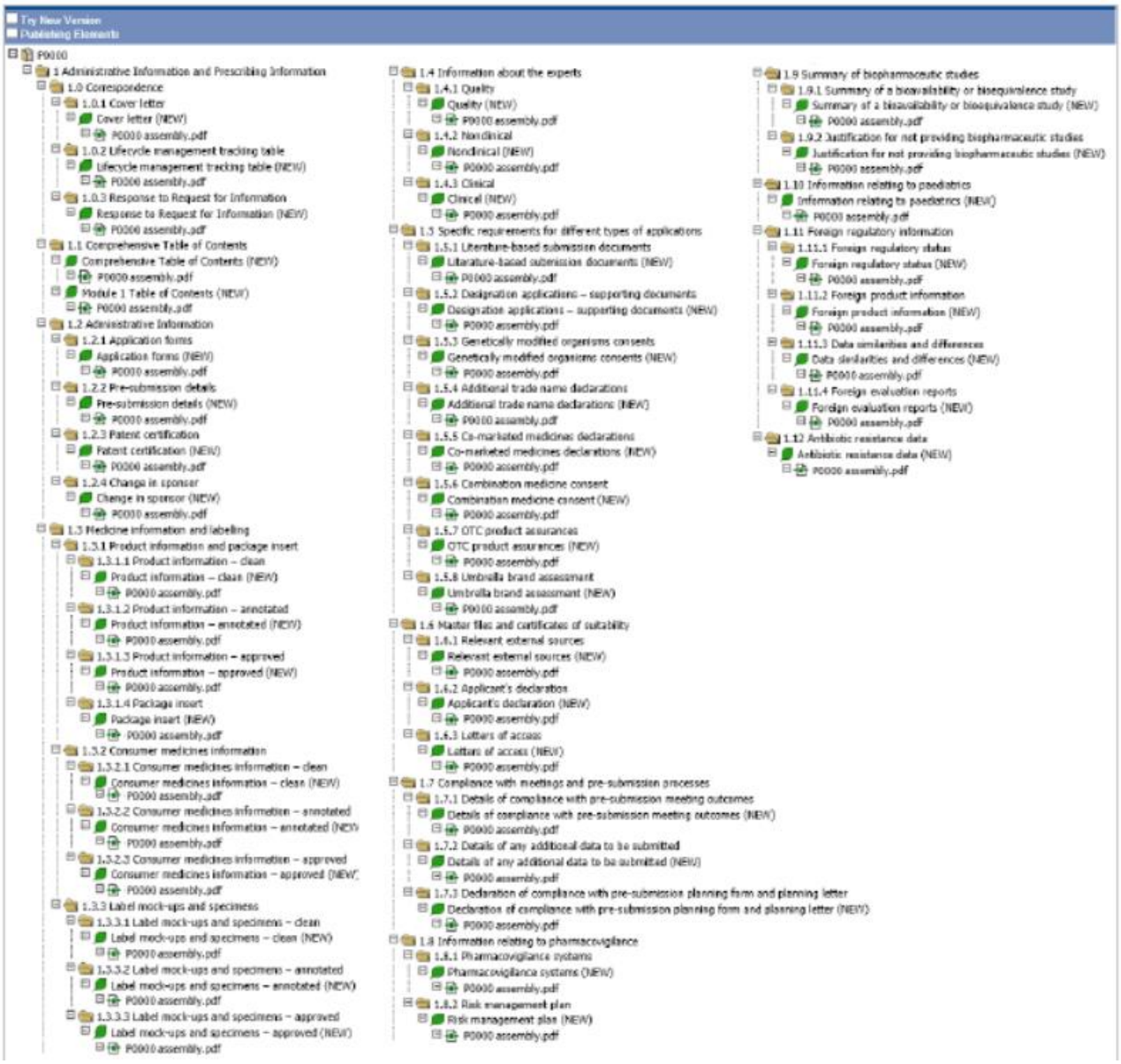
3.1.11.3 Data Administration Updates

The AU eCTD Module 1 Specification Version 3.1 provides the following updates to Data Administration:

Data Administration Table Name	Updates
Sequence Maintenance > Filing Type Values	The following new sequence types have been added: ▪ Provisional Registration - TGA initiated variation ▪ Notification ▪ CN ▪ Extension of Provisional Registration ▪ Duplicate
Sequence Maintenance > Filing Type Values	The following sequence type has been updated : ▪ Withdrawal filing type has been updated to be Product Withdrawal.
Submission Maintenance > Sequence Description Values	The following new Sequence Description value has been added: ▪ Provisional approval - rolling data submission - {date: d}
Submission Maintenance > Regulatory Activity Lead Values	The following new Regulatory Activity Lead value has been added: ▪ Prescription meds-biological

3.1.12 AU eCTD Module 1 Specification Version 3.1 Template Structure

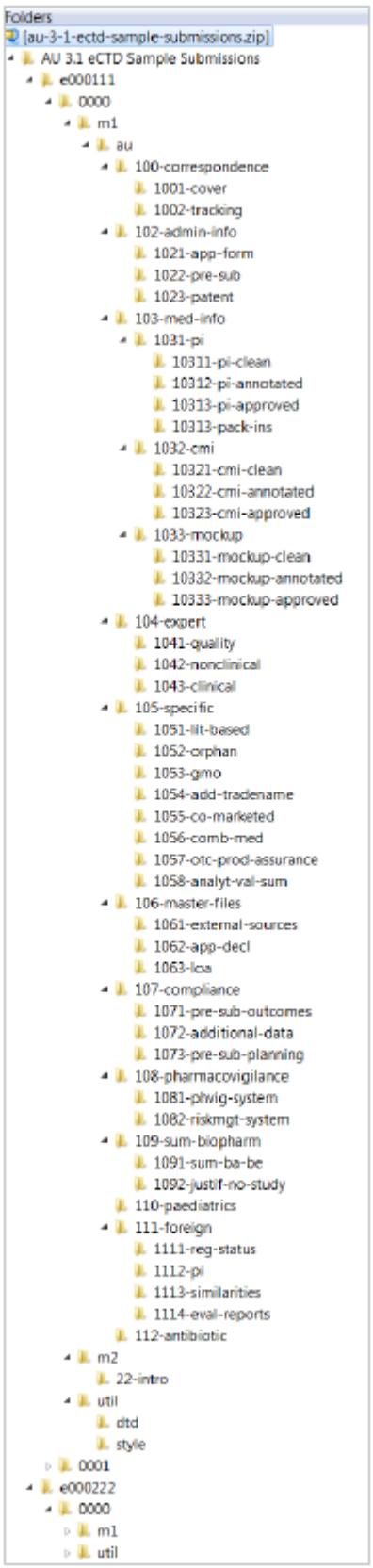
The following is an example of AU eCTD Module 1 Specification v3.1 template structure:



The ICH Common Technical Document (CTD) specifies the following:

- Module 1 should contain region specific administrative and product information.
- Module 3.2.R should be used for any additional drug substance and/or drug product information specific to Australia.

The following is a sample eCTD submission with three sequences:



The following table includes the recommended file formats that can be included in Module 1:

Section ID	Business Terminology	File Format
1.0 Correspondence		
1.0.1	Cover Letter XML form*	PDF Excel - XML
1.0.2	Lifecycle management tracking table	PDF
1.2 Administrative Information		
1.2.1	Application forms	PDF
Other		PDF

*NeeS envelope form

The following table describes the section identifier (ID), section name, XML-element and additional information, if applicable, for the M1 Headers and Elements:

Section ID	Section Name	XML-Element	Additional Information
1.0	Correspondence	`m1-0-correspondence`	N/A
1.0.1	Cover letter	`m1-0-1-cover`	N/A
1.0.2	Lifecycle management tracking table	`m1-0-2-tracking-table`	N/A
1.0.3	Response to request for information	`m1-0-3-response`	N/A
1.2	Administrative Information	`m1-2-admin-info`	N/A
1.2.1	Application forms	`m1-2-1-app-form`	N/A
1.2.2	Pre-submission details	`m1-2-2-pre-sub-details`	N/A
1.2.3	Patent certification	`m1-2-3-pat-cert`	N/A

Section ID	Section Name	XML-Element	Additional Information
1.2.4	Change in sponsor	m1-2-4-change-sponsor	N/A
1.3	Medicine information and labelling	m1-3-med-info	N/A
1.3.1	Product information and package insert	m1-3-1-pi	N/A
1.3.1.1	Product information - clean	m1-3-1-1-pi-clean	N/A
1.3.1.2	Product information - annotated	m1-3-1-2-pi-annotated	N/A
1.3.1.3	Product information - approved	m1-3-1-3-pi-approved	N/A
1.3.1.4	Package insert	m1-3-1-3-pack-ins	Section has been updated but element has been maintained to be consistent with previous specification version.
1.3.2	Consumer medicines information	m1-3-2-cmi	N/A
1.3.2.1	Consumer medicines information - clean	m1-3-2-1-cmi-clean	N/A
1.3.2.2	Consumer medicines information - annotated	m1-3-2-2-cmi-annotated	N/A
1.3.2.3	Consumer medicines information - approved	m1-3-2-3-cmi-approved	N/A
1.3.3	Label mock-ups and specimens	m1-3-3-mockup	N/A
1.3.3.1	Label mock-ups and specimens - clean	m1-3-3-1-mockup-clean	N/A
1.3.3.2	Label mock-ups and specimens - annotated	m1-3-3-2-mockup-annotated	N/A

Section ID	Section Name	XML-Element	Additional Information
1.3.3.3	Label mock-ups and specimens - approved	m1-3-3-3-mockup-approved	N/A
1.4	Information about the experts	m1-4-experts	N/A
1.4.1	Quality	m1-4-1-quality	N/A
1.4.2	Nonclinical	m1-4-2-nonclinical	N/A
1.4.3	Clinical	m1-4-3-clinical	N/A
1.5	Specific requirements for different types of applications	m1-5-specific	N/A
1.5.1	Literature-based submission documents	m1-5-1-lit-based	N/A
1.5.2	Designation applications - supporting documents	m1-5-2-orphan	N/A
1.5.3	Genetically modified organisms consents	m1-5-3-gmo	N/A
1.5.4	Additional trade name declarations	m1-5-4-trade-name	N/A
1.5.5	Co-marketed medicines declarations	m1-5-5-co-marketed	N/A
1.5.6	Combination medicine consent	m1-5-6-comb-med	N/A
1.5.7	OTC product assurances	m1-5-7-prod-assurance	N/A
1.5.8	Umbrella brand assessment	m1-5-8-umbrella	N/A
1.6	Master files and certificates of suitability	m1-6-master-files	N/A
1.6.1	Relevant external sources	m1-6-1-ext-	N/A

Section ID	Section Name	XML-Element	Additional Information
		sources	
1.6.2	Applicant's declaration	m1-6-2-app-decl	N/A
1.6.3	Letters of access	m1-6-3-loa	N/A
1.7	Compliance with meetings and pre- submission processes	m1-7-compliance	N/A
1.7.1	Details of compliance with pre-submission meeting outcomes	m1-7-1-pre-sub	N/A
1.7.2	Details of any additional data to be submitted	m1-7-2-add-data	N/A
1.7.3	Declaration of compliance with pre-submission planning form and planning letter	m1-7-3-planning	N/A
1.8	Information relating to pharmacovigilance	m1-8-pv	N/A
1.8.1	Pharmacovigilance systems	m1-8-1-pv-systems	N/A
1.8.2	Risk management plan	m1-8-2-risk	N/A
1.9	Summary of biopharmaceutic studies	m1-9-biopharm	N/A
1.9.1	Summary of bioavailability or bioequivalence study	m1-9-1-ba-be	N/A
1.9.2	Justification for not providing biopharmaceutic studies	m1-9-2-justification	N/A
1.10	Information relating to paediatrics	m1-10-paediatrics	N/A
1.11	Foreign regulatory information	m1-11-foreign	N/A
1.11.1	Foreign regulatory status	m1-11-1-status	N/A

Section ID	Section Name	XML-Element	Additional Information
1.11.2	Foreign product information	m1-11-2-pi	N/A
1.11.3	Data similarities and differences	m1-11-3-similarities	N/A
1.11.4	Foreign evaluation reports	m1-11-4-eval-reports	N/A
1.12	Antibiotic resistance data	m1-12-antibiotic	N/A

3.1.13 Creating a New Sequence in a Cross-Specification AU Application (AU v3.1)

The following procedure describes best practice guidance for the creation of AU submissions, according to the AU Module 1 eCTD v3.1 specification, within applications that have previous submissions compliant with the AU Module 1 eCTD v3.0 specification. Before starting the update process, make sure that all needed updates have been applied to the assembly compliant with AU eCTD Module 1 v3.0.

To make an AU eCTD application compliant with the AU eCTD Module 1 v3.1 specification, modify the Working View of the new lifecycle sequence for the application.

To make the application compliant, do the following:

1. To update the XML definition file to version 3.1:
    a. In the Working View, open the Publishing Settings dialog.
    b. Click XML Definitions.
    c. Remove the au-3-0 definition.
    d. Add the au-3-1 definition to the Selected XML Definitions.
    e. Click Save, and then click OK.
2. If you are submitting new content added under the 1.5 Specific requirements for different types of applications node by a new, append, or replace operation: in the Working View change the following leaf attributes under the 1.5.2 Designation applications - supporting documents folder.

    - Name: Designation applications - supporting documents
    - Abbreviated Name: Designation applications - supporting documents
    - Title: Designation applications - supporting documents

Note: The 1.5.2 Designation applications - supporting documents folder name will be the same for both Submitted view and Working view. If you apply a Replace or Append operation on the leaf under that folder and then apply Revert, the Leaf Name value will be changed according to AU eCTD Module 1 v3.0 specification and the Folder Name value will have the 1.5.2 Designation applications - supporting documents name according to AU eCTD Module 1 v3.1 specification.

3. The attributes of **the 1 Administrative Information and Prescribing Information** folder for the AU eCTD Module 1 v3.1 specification are different comparing to the AU eCTD Module 1 v3.0 specification. Enter the appropriate values for the following folder attributes:
    a. Submission or Application Number(s)
    b. Submission Mode
    c. Contact Email
4. After the migration, the 1.3.1.3 Package insert folder number will be changed to be 1.3.1.4.
5. The following values will be migrated accordingly in the Folder Information:

The name of the field where the value is stored before the migration	The name of the field where the value is stored after the migration
eSubmission Identifier	e-Identifier
Applicant	eBS Client ID
Australian Approved Name(s)	Approved Name(s)
Product Name	Trade Name(s)
ARTG Number	ARTG Number(s)
Sequence Description	Sequence Description
Sequence Number	Sequence Number
Related Sequence Number	Related Sequence Number
Regulatory Activity Lead	Regulatory Activity Lead
Sequence Type	Sequence Type

3.1.13.1 Creating an Assembly Based on the AU Module 1 NeeS v2.0 Template

This procedure guides you though the steps to create and publish an Assembly based on the AU Module 1 NeeS v2.0 Template.

1. Create a new Standalone Assembly based on the AU Module 1 NeeS v2.0 Template.
2. In the Publishing Settings, make sure that the au-nees-2-0 DTD is selected in the **XML Definitions** > **Selected XML Definition Files** field.
3. Fill in the Envelope data on the **M1** folder.
4. Where needed, assign documents to the necessary leafs.
5. Publish the assembly to generate an envelope.xml file with the **Publish eCTD/Electronic > XML Only** option selected.
    a. Check the **Publish Job Details** to make sure that there are no errors.
    b. Make sure that the location of an envelope.xml file is the following: m1\au\100-correspondence\1001-cover\.

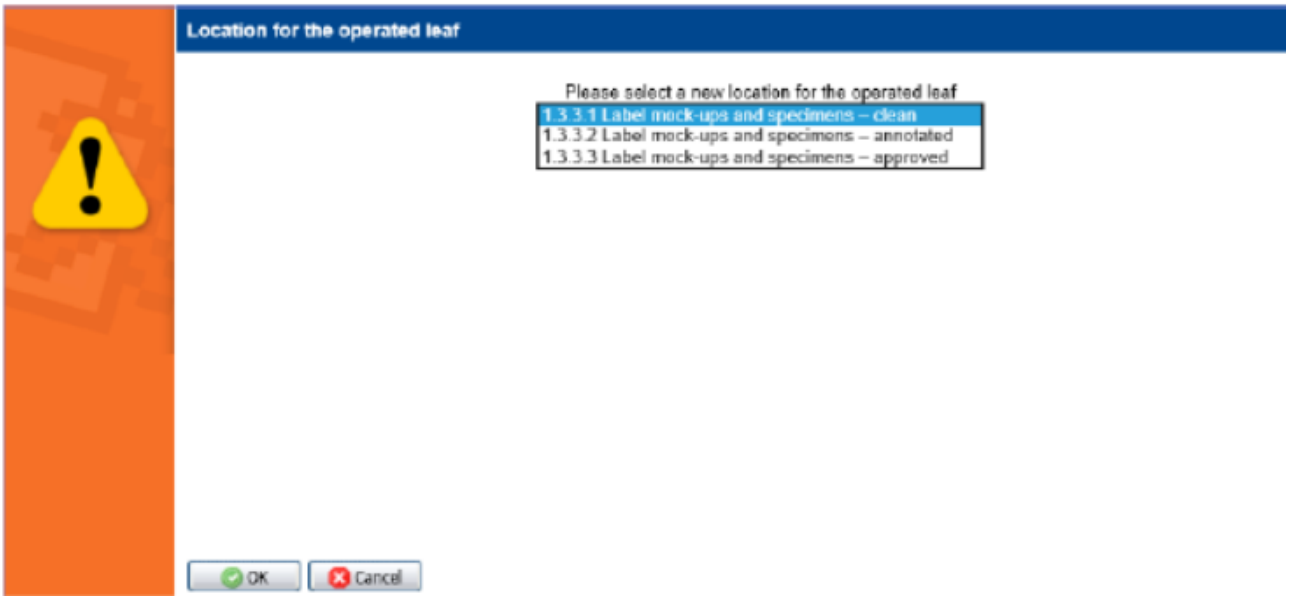
c. Make sure that the envelope is of version 1.0 and contains all the fields according to the specification.

6. Rename the envelope.xml file, if needed.
7. Assign the generated envelope.xml file to the leaf under the **1.0.1 Cover Letter** folder.
8. Navigate to the **More > Publishing Settings Library > TOCs** tab and click the **Create TOC Type** icon.
9. Go to the **More** menu and perform **Prepare to Publish** with the **Generate TOCs** option selected.
10. Publish the assembly with the **Publish eCTD/Electronic > All Leaf Elements** option selected.

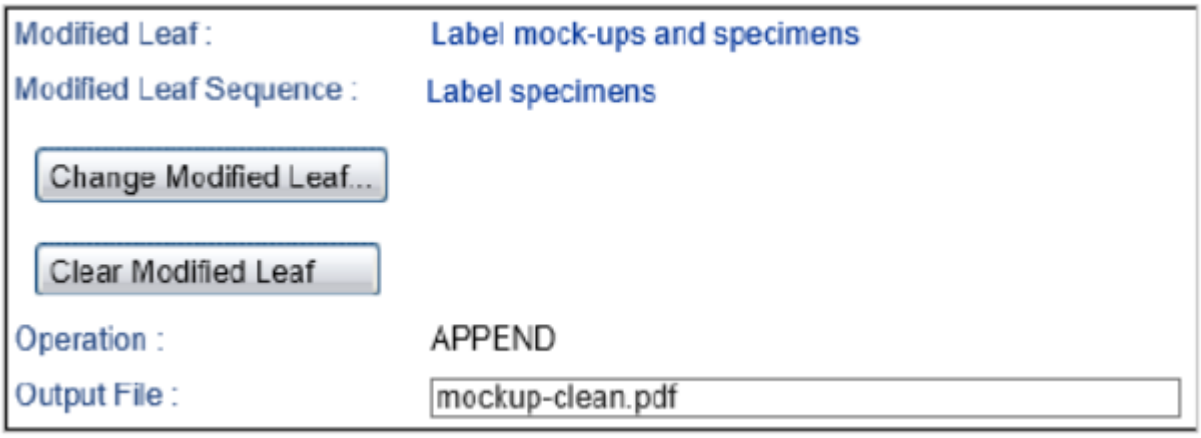
3.1.13.2 Append/Replace Operations within a Cross-Specification Application AU

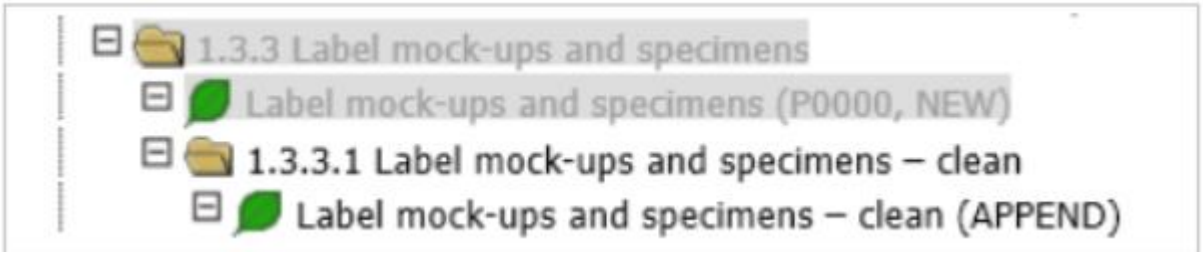
Important: Performing a replace operation using RIM drag-and-drop functionality is not recommended, as this will cause undesirable results.

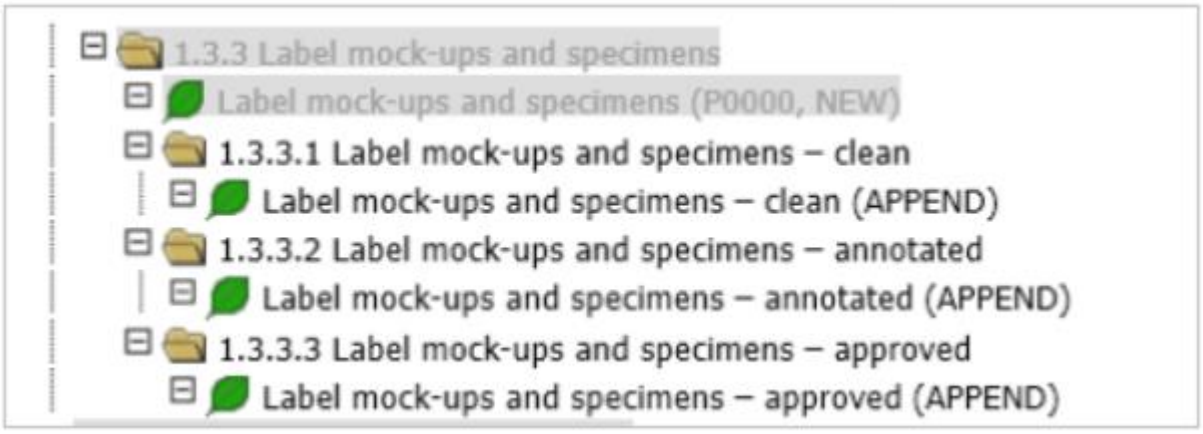
The AU Module 1 eCTD Specification Version 3.1 includes changes to the structure of the XML backbone, and it particularly affects the following sections in the original 3.0 template: 1.3.1.3 and 1.3.3.
After any lifecycle operation is invoked from a leaf that was originally submitted in one of those locations, you will be prompted to specify a new location for the append/replace leaf. Choose the location and click **OK**.



The operation automatically creates a new folder and leaf that is required, with the appropriate operation. Folder Extensions will be assigned automatically, if needed. The created leaf Name will be followed by **(REPLACE)** or **(APPEND)** according to the selected operation.







3.1.14 Updating an AU Submission to Migrate to v3.0

For an application that has a submission that was compliant with an AU Module 1 eCTD specification version before v3.0, create an AU submission that is compliant with the v3.0 specification.

3.1.14.1 Electronic Lodgement Cover Sheet (1.0.0) and Certificates of Suitability (1.6.4) Removed

The v3.0 specification includes changes to the structure of the XML backbone. The v3.0 specification does not include the following elements:

- m1-0-0-elodgement (corresponded to the 1.0.0 Electronic lodgement cover sheet section in the AU v0.90 template)

- m1-6-4-cert-suit (corresponded to the 1.6.4 Certificates of suitability section in the AU v0.90 template)

Do not perform operations on these leafs. Performing operations on these leafs will cause invalid XML.

3.1.14.2 Creating a New Sequence in a Cross-Specification AU Application

To make an AU eCTD application compliant with the v3.0 AU Module 1 eCTD specification, modify the Working View of the new lifecycle sequence for the application.

To make the application compliant, do the following:

1. To update the XML definition file to version 3.0:
    a. In the Working View, open the **Publishing Settings** dialog.
    b. Click **XML Definitions**.
    c. Remove the au-0-90 definition.
    d. Add the au-3-0 definition to the Selected XML Definitions.
    e. Click **Save**, and then click **OK**.
2. If you are submitting new content added under the **1.5.8** node by a new, append, or replace operation, in the Working View change the following attributes of the 1.5.8 Analytical validation summary folder:
    a. **Name**: Umbrella brand assessment
    b. **Abbreviated Name**: Umbrella brand assessment
3. If you are submitting new content added under the **1.5.8** node by a new, append, or replace operation, in the Working View change the following attributes of the leaf submitted under the **1.5.8** node in the current sequence:
    a. **Name**: Umbrella brand assessment
    b. **Abbreviated Name**: Umbrella brand assessment
    c. **Title**: Umbrella brand assessment
    d. **Output File**: umbrella-brand-assess.pdf

Make sure that you do not perform any operations on the following leafs, because the v3.0 specification does not include them:

- m1-0-0-elodgement
- m1-6-4-cert-suit

3.1.15 Updating Existing TH Submissions Migrated to v1.0

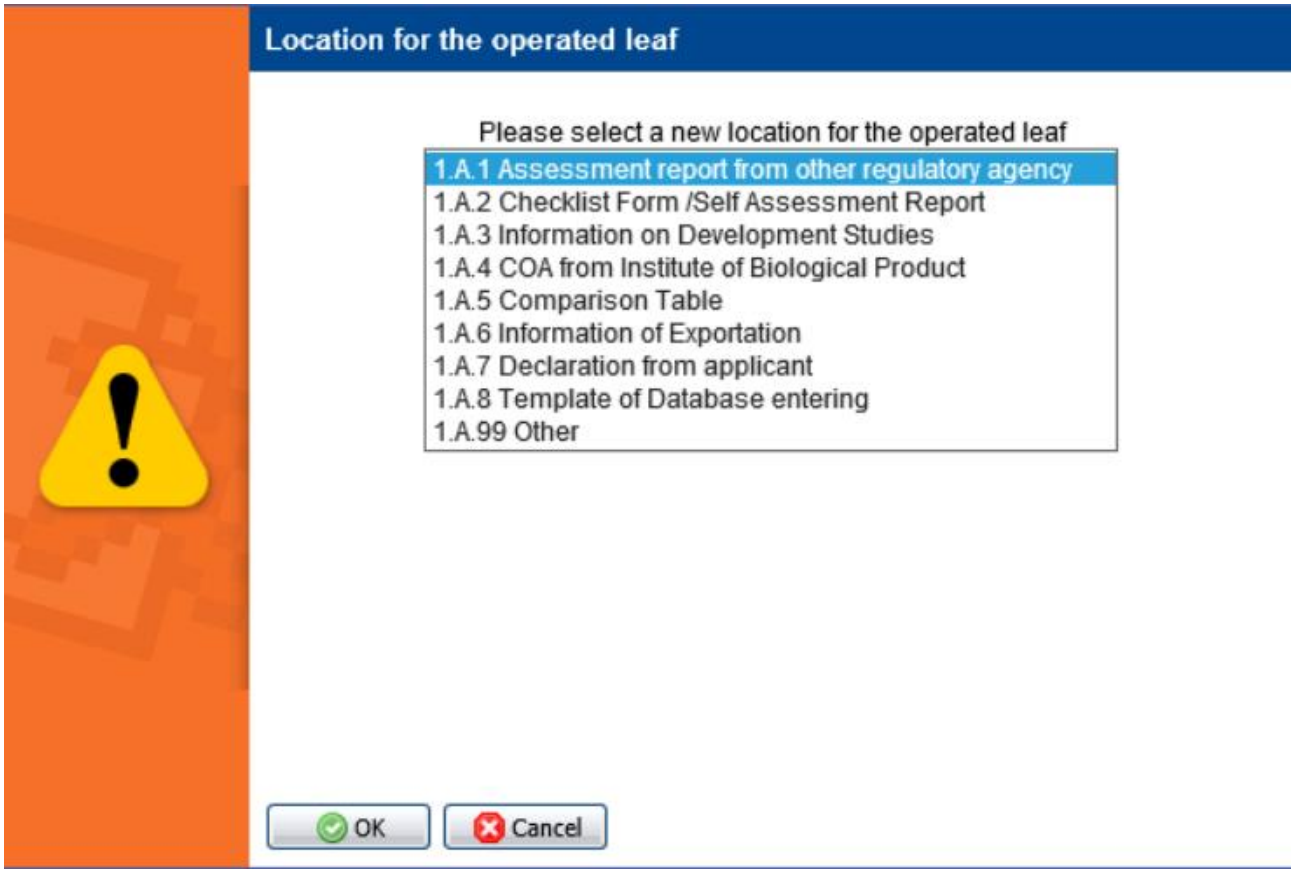
This document provides Best Practice guidance for the creation of TH submissions, according to the TH Module 1 eCTD v1.0 specification, within applications that have previous submissions compliant with the TH Module 0.92 eCTD specification.

3.1.15.1 Append/Replace/Withdraw Operations within a Cross-Specification Application

Important: Performing a replace operation using Ennov InSight drag-and-drop functionality is not recommended, as this will cause undesirable results.

The TH Module 1 eCTD Specification Version 1.0 includes changes to the structure of the XML backbone, particularly to the locations where submitted documents can be referenced. This affects **Additional Data** section in the original 0.92 template.

After any lifecycle operation is invoked from a leaf that was originally submitted in **Additional Data** location, you will be prompted to specify a new location for the append/replace/delete leaf. Choose the location and click **OK**.



The operation automatically creates any new folder and leaf that is required, with the appropriate operation. The new leaf will contain the Modified Leaf attribute set to the original leaf.

3.1.15.2 Creating new Sequences within a Cross-Specification Application TH

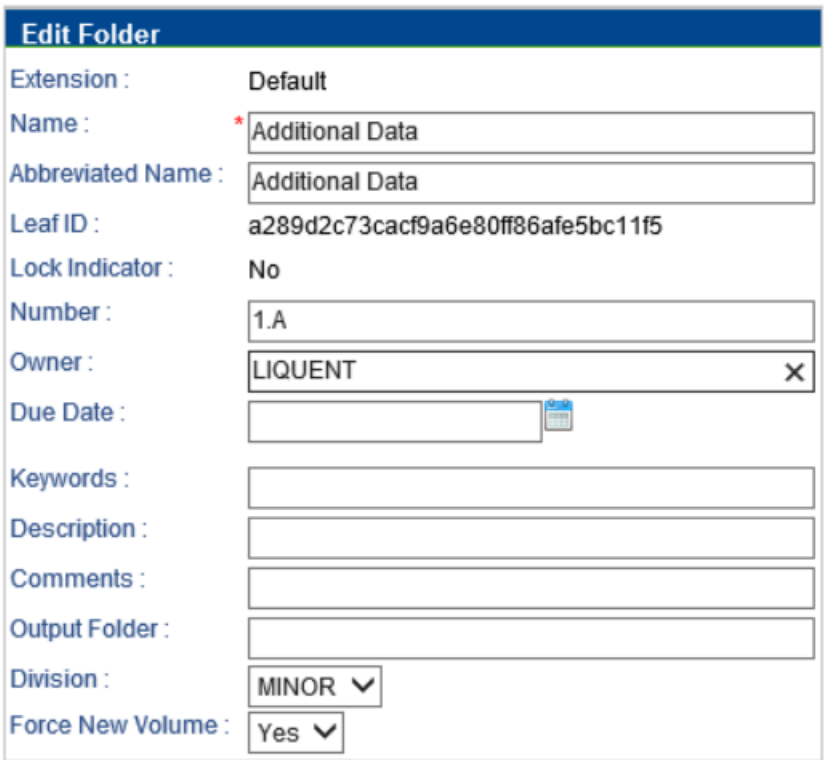
Using the **eCTD Wizard** to create or update a working assembly after the switch to the v1.0 DTD is not supported and can create undesired results. For any subsequent sequences, the **eCTD Wizard** can be used to update a manually created assembly only.

To create new Sequence based on the TH Module 1 eCTD Specification Version 1.0:

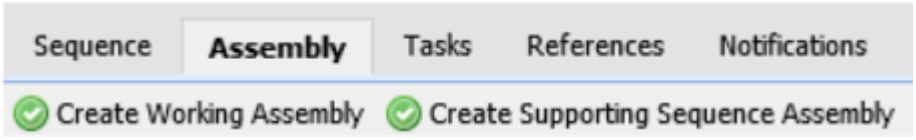
1. Open the Submitted view of the TH eCTD application that is associated with the assembly.
2. Unlock the **Submitted View**.

Note: If you have previously associated your working assembly with an application, the Submitted View cannot be unlocked.

3. Click the Additional Data folder.
4. Navigate to the **More** list and click **Change Type**.
5. In the **Extensions** list click Default. The warning message appears stating that the changing the type will erase publishing information.
6. Click **OK**.
7. Set the **Number** attribute of the Additional Data folder to be **1.A** and click **Save**.



8. Lock the modified Submitted View.
9. Create a new Sequence within an existing Application. Switch to the **Assembly** tab and click **Create Working Assembly**.



10. After the new working assembly is created and before making any modifications:
    a. Go to the **Publishing Settings Library** (Edit Publishing Settings Library icon in the menu).
    b. Open **Publishing Settings** for editing, remove th-0-92 from the **Selected XML Definitions** list and add th-1-0.
    c. Click **Save**.

3.1.15.3 Locations Configured for Cross-Section Append/Replace/Withdraw TH

By default, the following configuration is set:

Source Leaf Location (DTD v0.92)	Valid destination (DTD v1.0)
Additional Data	1.A.1 1.A.2 1.A.3 1.A.4 1.A.5 1.A.6 1.A.7 1.A.8 1.A.99

3.1.15.4 Reverting Lifecycle Operations

Reverting lifecycle operations performed in section **Additional Data** will remove any folders created as part of the replace/append/delete operation. Folders will not be removed if they contain other elements.

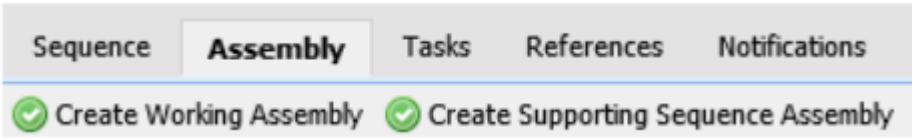
Revert of an append operation is invoked from the original leaf, which resides in the original (TH 0.92) location. Revert of the replace/delete operation is invoked from the replace/delete leaf, which resides in the new (TH 1.0) location.

3.1.16 Updating Existing ZA Submissions Migrated to v2.1

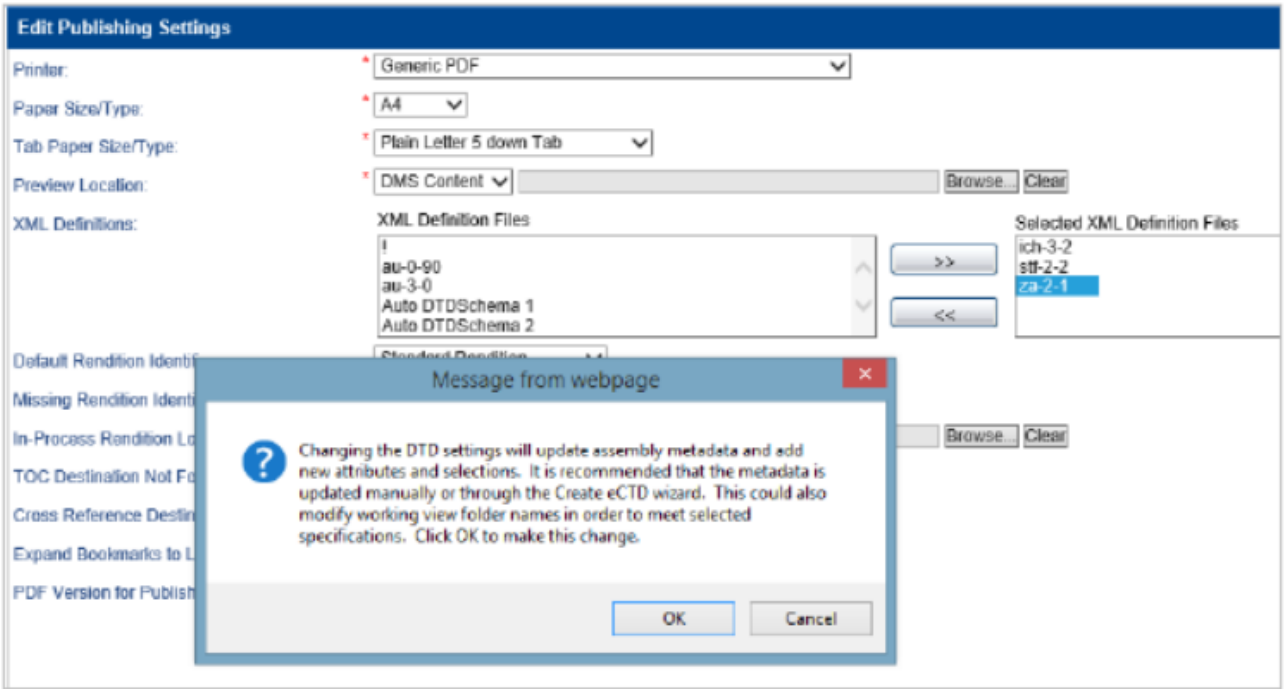
Using the **Create eCTD Wizard** to create a working assembly using the 2.1 DTD is not supported and can create undesired results. For any subsequent sequences, the **eCTD Wizard** can be used to update only manually created assemblies.

To create a new Sequence based on the ZA Module 1 eCTD Specification Version 2.1:

1. Create a new Sequence within an existing Application. Go to the **Assembly** tab and click **Create Working Assembly**.



2. After the new working assembly is created and before making any modifications: go to **Publishing Settings Library** (click Edit Publishing Settings Library). On the **XML Definitions** tab, remove za-1-0 from the **Selected XML** Definitions list and add za-2-1.
3. Click **Apply**.



4. After the new XML Definition File is applied, refresh the assembly tree. Applying the za-2-1 XML Definition File updates the assembly according to the 2.1 specification: Values in extended attributes
5. The **Create eCTD Wizard** can now be used for the Sequence. After the new za-2-1 XML definition file is applied, the changes within the current assembly cannot be rolled back. If it is necessary to roll back the changes, the working assembly must be deleted and recreated.

3.2 Module 2 – Summaries

Sections 2.3.S Drug Substance, 2.3.P Drug Product and 2.3.7 Summary of Clinical Efficacy have additional attributes. If these values were not mapped in the template, the user should select these folders and complete their attributes during execution of the Wizard or on the assembly folders themselves.

The attributes for substance and manufacturer for 2.3.S Drug Substance and indication attribute for 2.7.3 Summary of Clinical Efficacy are required to produce valid XML when those sections are included in the submission, the Drug Product additional attributes are optional. When using the Wizard, it will only prompt once for Drug Substance and Drug Product information and duplicate the information in both Modules 2 and 3, as well as once for indication if 2.7.3 and 5.3.5 are included and duplicate the information in each section. If separate values are desired for the different Modules, for example, if all manufacturers are consolidated in the Module 2 summaries under a single section, but broken into separate sections in Module 3, the Wizard can be executed iteratively to select and provide values specific to the desired Module. There is no requirement that the values of the attributes be the same between Modules 2 and 3.

The default file names for each of the leafs in these sections are as defined in the ICH specification. When multiple drug substance, drug product or clinical indications are being provided, the file name attributes for those leafs should be adjusted to reflect the specific attributes associated with those attributes per the Guidance:

Where there are more than one drug substance and/or manufacturer, separate files should be provided for each. The file name should always include the name of the drug substance e.g., ranitidine hydrochloride through inclusion of the International Non-proprietary Name to give 'ranitidine-hydrochloride'. Similarly, for manufacturer, the file name should always include the name of the manufacturer e.g., ranitidine-hydrochloride-manufacturer-1.pdf. Where there is more than one manufacturer, the drug substance file should be repeated but with an indication of each manufacturer concerned included in the file name, the first instance e.g., 'drug- substance-1- manufacturer-1.pdf' and the second 'drug-substance-1-manufacturer-2.pdf The file name should always include the name of the drug product through inclusion of the name of the form/strength to give e.g., 'drugproduct- tablet-5mg'. Where the application is for a complex presentation with multiple components the file name should identify additional items such as the component. Refer to regional guidance for definition of what constitutes a drug product and the acceptability of more than one drug product in an application. Where more than one drug product is acceptable in an application, a separate file should be provided for each drug product. The file name should always include the indication being claimed (abbreviated if appropriate) e.g., 'summary-clin-efficacy-asthma'. Where there is more than one indication (e.g., asthma & migraine) then the first indication has a file name 'summary-clin-efficacy- asthma' and the second 'summary-clin-efficacy-migraine'. Typically, this logical document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.

After the assembly is created, select the appropriate leaf elements under 2.3.S, 2.3.P, and/or 2.7.3 and edit them to update the file names as desired. It is not necessary that the descriptive information provided in the file name exactly match the full attribute value provided for the section. An abbreviated version of the information may be more appropriate to maintain a shorter file name.

When providing paper to accompany the eCTD, a sample CTD TOC is included under the 2.1 Module 2 Table of Contents folder in the template. Prior to generating this, the TOC Range should be set correctly to ensure all desired entries are available.

3.3 Module 3 – Quality Information

Sections 3.2.S Drug Substance, 3.2.P Drug Product, 3.2.P.4 Excipients, and 3.2.A.1-3 have additional attributes. If these values were not mapped in the template, these should be populated during execution of the Wizard or the user should select these folders and complete their attributes.

The substance and manufacturer attributes for 3.2.S Drug Substance are required to produce valid XML when that section is included in the submission, the Drug Product, Excipient and Appendix attributes are optional. When using the Wizard, it will only prompt once for Drug Substance and Drug Product information and duplicate the information in both Modules 2 and 3. If separate values are desired for the different Modules, for example, if all manufacturers are consolidated in the Module 2 summaries under a single section, but broken into separate sections in Module 3, the Wizard can be executed iteratively to select and provide values specific to the desired Module. There is no requirement that the values of the attributes be the same between Modules 2 and 3.

The attribute values provided for sections 3.2.S, 3.2.P, 3.2.P.4, and 3.2.A.1-2 are used when creating the output paths for the child leafs in those sections. The system automatically converts upper case characters to

lower case and spaces, periods and underscores to hyphens when building these paths, so users can provide attribute values with upper case characters etc., for the values that will appear in the XML, and the system will automatically create valid output paths. However, the system will not truncate the values if they result in paths that exceed the 64 character/folder, 230 character for full path limit, as it cannot assume a logical abbreviation. The system will log a warning for paths that exceed the limit and the user can override the use of the attributes by populating a value for the output folder on the related section. The system will then ignore the additional attributes when building the path and add the value of the output folder attribute to the end of the system-generated path. There have been challenges seen with longer paths at regulatory agencies due to truncation of paths when moving submissions on fileshares and creating media. To resolve this, the latest eCTD specification (v3.2.2) has been udpated to clearly indicate that the attribute values provided as meta-data in the XML do not need to match the folder names in these sections and that abbreviations can be used. To prevent RIM from using the attribute values to create folder names, populate the Output folder attribute of these folders as described below:

- 3.2.S Drug Substance: Output Folder=32s-drug-sub/abb-sub-abb-mfg, where abb-sub is the abbreviated substance name and abb-mfg is the abbreviated manufacturer name
- 3.2.P Drug Product: Output Folder=32p-drug-prod/product-1, where product-1 is the abbreviated product information you want to include in the folder path
- 3.2.P.4 Excipient: Output Folder=32p4-contr-excip/excipient-1, where excipient-1 is the abbreviated excipient information
- 3.2.A.1 Facilities and Equipment: Output Folder=32a1-fac-equip/manufacturer, where manufacturer is the abbreviated manufacturer information
- 3.2.A.2 Adventitious Agents Safety Evaluation: Output Folder=32a2-advent-agent/variable, most like where variable is the desired combination of substance, product, manufacturer and dosage information to provide differentiation between documents in this section.

In Section 3.2.P.4, three sample structures are included in the assembly template to reflect the different requirements for compendial vs. non-compendial vs. human, novel or animal excipients. Comments are populated on these folders to assist with completion of these sections. The Wizard can be executed iteratively for each type of Excipient (compendial vs. non-compendial) to ensure correct capture of the meta-data for each type of Excipient.

Sections 3.2.A.1 and 3.2.A.2 have the optional attributes of substance, manufacturer, product, and form. The specification indicates that the necessary information to ensure uniqueness is added to the output path when there is more than one set of information provided for these sections. There are comments on these folders to assist with the creation of these sections. Section 3.2.A.3 does not have additional attributes in the XML, but when there is more than one excipient, this information is added to the output path. The system will automatically build this information into the path if this folder is duplicated for each excipient and the excipient attribute populated.

3.4Module 4 – Nonclinical Study Reports

The Module 4 folder allows the user to define how study reports in this section should be organized in the XML and in the directory structure, as well as the default value for the subject matter (file-tag name) to be used for all leaf elements if STFs are created.

Any leaf elements left as Default leafs will inherit their subject matter from the value on the Module 4 folder during publishing. Any of these defaults may be overridden on the Study Report folders or leafs by explicitly setting their types and values.

The Assembly template provided includes a sample STF-creating nonclinical study report in section 4.2.1.1 Primary Pharmacodynamics. If STFs are being provided and default values were not mapped in the template for Full Report Title and Report Number, these should be completed prior to publishing. This folder can be duplicated for each study included in the submission and moved to the appropriate section. When submitting STFs in the US, the operation on the STF folder should be set to append on subsequent sequences in which components of the report are being operated on. The EU, Japan and Canada have indicated that they will accept STFs, but that they are not mandatory. Confer with the appropriate regulatory authority to determine the approach to be used when submitting STFs in these other regions. If STF category information (species, route of administration, duration) is captured in the DMS, it may be useful to modify the assembly template to include sample studies in Sections 4.2.3.1, 4.2.3.2, and 4.2.3.4.1 and set mappings for species, route & duration per guidance since these are the only study types in Module 4 that require this additional category information.

A single leaf is included in the sample study folder with its subject matter value set to “nonclinical-data” as specified by the US STF specification. If STFs are being submitted in another region, this value should be modified to pre-clinical-study-report as nonclinical-data is a US-only file-tag name. If the study report consists of more than one file, additional leafs can be added simply by right clicking on the study report folder and choosing Add Leaf. All leafs included in the folder will be reflected in the resulting STF.

If, in lieu of STFs, node-extensions are being used to differentiate one study from another, select the Module 4 folder and change the Study Organization in XML setting to node-extension. All study report folders should stay as “Study Report” folder types. The study folder names will be used for the node-extension title. All leafs included in the folder will be added to the XML under the node-extension element. Node extensions should only be used at the lowest level of the assembly, use of node extensions at higher levels in the assembly will result in errors during publishing as these will result in invalid XML.

Please note different regulatory authorities have different stances on using node-extensions. Ennov recommends consulting with the reviewing agency to determine the acceptability and applicability of node extensions.

3.5 Module 5 – Clinical Study Reports

3.5.1 CSR Structure for STFs

Module 5 includes the clinical study reports, case report forms, and study data files.

The Module 5 folder enables the user to define how study reports in this section are organized in the XML and in the directory structure. The Module 5 folder also sets the default value for the subject matter (file-tag name) to be used for all leaf elements, if STFs are created. Any leaf elements kept as Default leaf elements inherit subject matter from the value in the Module 5 folder during publishing. Users can override any of these defaults in the Study Report folders or leaf elements by explicitly setting their types and values. Such

inheritance is useful if it can be mapped to a DMS attribute rather than using a static value, because a number of subject matter values are likely within a given study report.

The Assembly template provided includes a sample clinical study report in section 5.3.1.1 Bioavailability Study Reports. The template also includes ISS and ISE structures in 5.3.5.3 and a separate E3 CSR Assembly template used by the Create eCTD Wizard. Additional study report templates can be created for each section and associated with their respective sections for the Create eCTD Wizard to apply as needed. If STFs are provided and default values are not mapped in the template for Full Report Title and Report Number, the values should be completed before publishing. If the Create Study Report Wizard is used to add studies to the assembly, the default name displayed for each study in the wizard is the same as the section number to which the study will be added. Users should update the Name to reflect each study and provide the Full Report Title, Report Number, and the additional type of control category information for studies in 5.3.5.1.

When submitting STFs in the United States, users should set the operation on the STF folder to append subsequent sequences for which components of the report are being operated. The European Union, Japan, and Canada regulatory agencies indicated that they will accept STFs, but they are not mandatory. Confer with the appropriate regulatory authority to determine the approach to be used when submitting STFs in these regions. If STF category information (type of control) is captured in the DMS, modifying the assembly template to include sample studies in Section 5.3.5.1 and setting mappings for type of control according to guidance may be useful, because this is the only study type in Module 5 that requires this additional category.

A full ICH E3 study report structure is included in the sample study report that includes folders for organizing the appendices and the subject matter value set on each leaf according to the STF Specification v2.6.1. The additional Appendix folders for Study Information (Appendix 16.1) and Patient Data Listings (Appendix 16.2) do not affect the output directory structure or the XML. The folders simply make the study report more manageable in the Assembly. To minimize redundant data entry, the Case Report Forms (Appendix 16.3) and Individual Patient Data Listings (Appendix 16.4) folders have special folder types applied to them.

3.5.2 Case Report Forms

Module 5 includes the clinical study reports, case report forms, and study data files.

As discussed with the FDA, the sample study report includes Case Report Forms in Appendix 16.3 instead of section 5.3.7 of the eCTD. This facilitates inclusion in the STF and grouping with the rest of the study report information. When Case Report Forms are provided, each CRF includes an additional site-information attribute in the STF. When the Case Report Forms folder in the assembly is structured as it is in the sample study with all CRFs are organized into Site folders, the system automatically uses the name of the site folder to complete the site information attribute for each case report form. The system also sets the file-tag name by using the Subject Matter attribute of the Case Report Forms folder, which is particularly useful if the CRFs are already structured by site in the repository. All CRFs can be added to their assembly by dragging and dropping the site folders into the assembly. The system automatically creates a leaf for each file, uses the name of the file as its leaf name, and uses that value for the output file name. By default, all CRFs are output directly in the study report folder with the other study content. If needed, users can create an additional

folder or folders to further organize the files by populating the Output folder attribute on the Case Report Forms and/or Site folders. Any values entered here are added to the default Ennov InSight-created path.

If users want to include these in section 5.3.7 of the eCTD and organize using node extensions instead of including CRFs with the study report, the CRF folder in the study report can be moved to section 5.3.7 and the folder type changed to node extension. All leaf elements included in the folder are added to the XML under the node-extension element. Use node extensions only at the lowest level of the assembly. Use of node extensions at higher levels in the assembly will create an invalid XML, resulting in errors during publishing. The system uses the folder name for the node-extension title, so users should modify the Name of the folder to indicate the study report number. Please note that different regulatory authorities have differing opinions about using node-extensions. Ennov recommends consulting with the reviewing agency to determine the acceptability and applicability of node extensions.

3.5.3 Study Data Files

Module 5 includes the clinical study reports, case report forms, and study data files.

The FDA Study Data Specification indicates that Study Data files for all study reports within a module should be organized in a datasets folder directly under the module folder, and further organized by Study number and dataset type within the datasets folder. The Individual Patient Data Listings folder in the sample study report appendix is a Study Data folder. This folder organizes the datasets with the study report in the Assembly, while automatically placing them in the correct output directory during publishing. The Study Data folder type controls the location of leaf elements in a different directory structure than the other study report components during publishing. When the top level folder has a Dataset type value of “datasets and associated files”, its child folders provide the additional directory structure needed to organize the different dataset types. It also provides the subject matter values for the leaf elements within them to be used as the file-tag names for those files in the STF.

The sample study report includes a define.xml file under each dataset type: analysis, tabulations and listings. These are set as Study Report Leaf elements, because they should not inherit subject matter values from their parent folders. All other actual dataset files can be left as default to inherit their subject matter from their parent folders.

One or more XPT files can be dragged and dropped to their appropriate subtype. A leaf will be created for each file, which is automatically set to **Use Native File=Yes**. Additionally, if a define.pdf is provided instead of a define.xml file, users should edit this sample leaf to set **Use Native File** to **No** and update the Output file name to define.pdf. The structure provided includes a single leaf for the Annotated Case Report form outside the dataset subfolders.

If instead, the leaf is included with the specific dataset types, it may be moved or duplicated and moved to the appropriate subfolder(s). If SDTM Datasets are provided, any additional supportive files such as stylesheets, can also be added to the structure and automatically referenced by the STF. The sample Data Definition leaf can be duplicated and updated with the appropriate name and output file name for these additional files to ensure the proper subject matter values are used.

3.5.4 CSRs organized with Node Extensions

Module 5 includes the clinical study reports, case report forms, and study data files.

If node-extensions are used to differentiate one study from another instead of STFs, select the Module 5 folder and change the Study Organization in XML setting to node-extension. All study report folders should remain Study Report folders. The folder name is used for the node-extension title. All leaf elements included in the folder are added to the XML under the node-extension element. No changes to the individual leaf elements of the study report are needed.

Node extensions should only be used at the lowest level of the assembly. Use of node extensions at higher levels in the assembly result in errors during publishing, because they result in invalid XML. Please note that different regulatory authorities have different opinions about the use of node-extensions. Ennov recommends consulting with the reviewing agency to determine the acceptability and applicability of node extensions.

3.6Transitioning to Valid Values v3.0 and Study Data Specification v2.0

The US Food and Drug Administration (FDA) has updated the Valid Values list to version 3.0 (effective 30 April 2013), removing some file-tags and adding others. The changes in the Valid Values update concern file-tag elements for analysis and tabulation datasets.

The previous file-tag **analysis-dataset** has been replaced by two new values:

- analysis-dataset-adam
- analysis-dataset-legacy

The previous file-tag **data-tabulation-dataset** has been replaced by three new values:

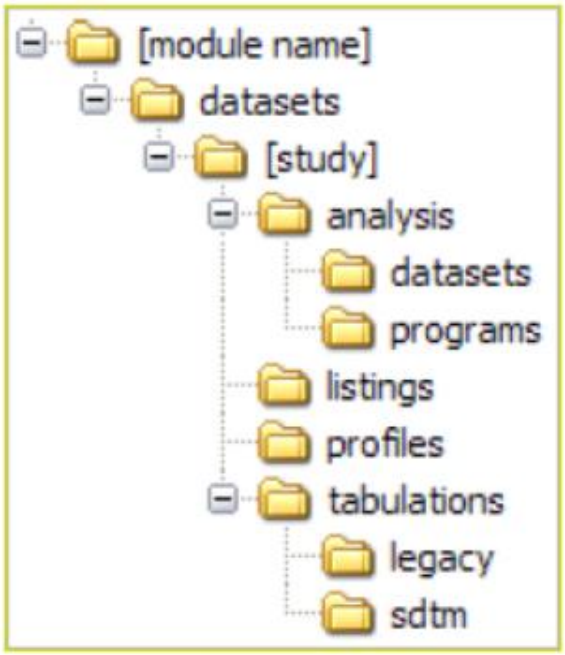
- data-tabulation-dataset-legacy
- data-tabulation-dataset-sdtm
- data-tabulation-dataset-send

In addition to the file-tag changes, FDA had also updated the Study Data Specification to version 2.0 (July 2012). The Study Data Specification shows an updated folder structure that accommodates the new dataset types under the [module]/datasets output folders.

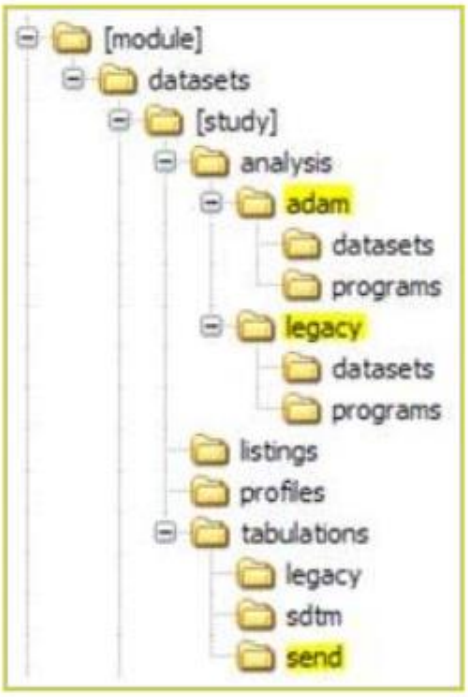
This Best Practices document has been created to help you modify existing FDA eCTD submissions in RIM Publisher so that you can produce both the new file-tags and the new published output folder structure.

The following images show the differences between a Study Data v1.5.1 Folder Structure and a Study Data v2.0 Folder Structure:

Study Data v1.5.1 Folder Structure



Study Data v2.0 Folder Structure



3.6.1 Adding or Modifying Datasets in a Lifecycle Submission

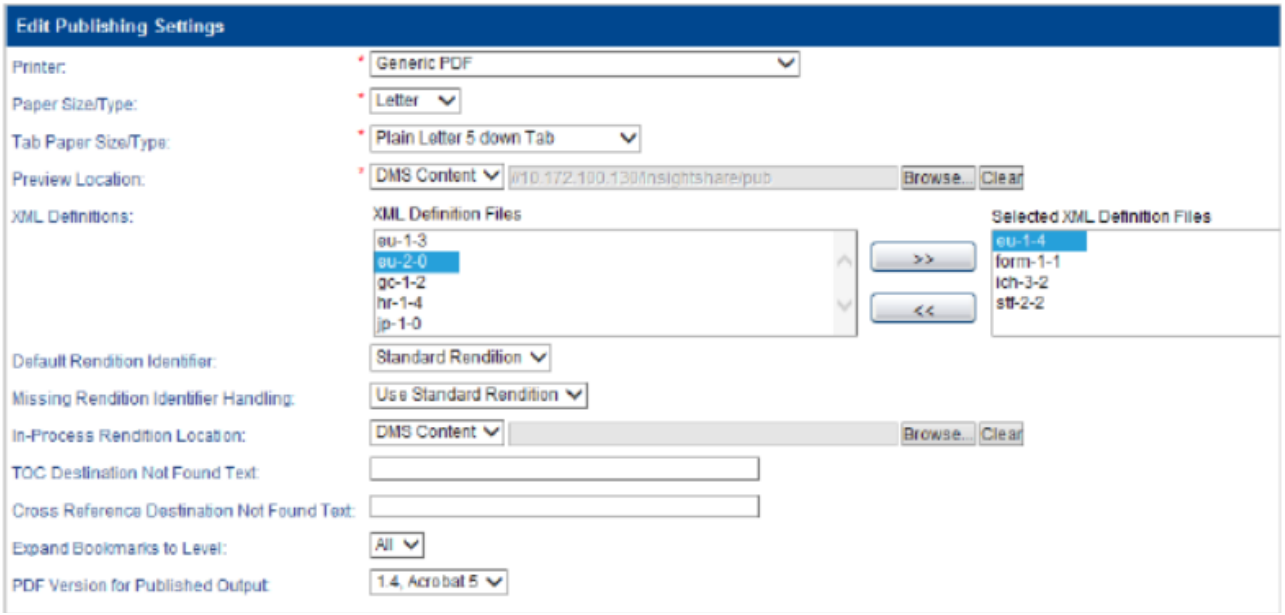
In a new lifecycle sequence for an existing US eCTD, all previous leafs and folders display as gray. In order to create output compliant with Valid Values v3.0 and Study Data Specifications v2.0, some modifications to the dataset folders must be performed in the Working View.

Please note the Individual Patient Data Listings folder is an Extension type of Study Data. The Dataset Type is datasets-and-associated-files. This special folder instructs RIM Publisher to place the published datasets under the m5/datasets/[study] folder structure, rather than under the 5.3.x folder structure with the rest of the study report leafs.

Existing CSR from previous lifecycle sequence, using older Valid Values and Study Data structure:

To modify datasets in a lifecycle submission, first update the Study Tagging File XML Definition to version 3.0:

1. From the **Working View**, open the **Publishing Settings** dialog.
2. Click **XML Definitions**.
3. Remove the stf-2-2 definition and add the stf-2-2-3-0 definition to the **Selected XML Definitions**.
4. Click **Save**. A confirmation message window appears.
5. Click **OK**

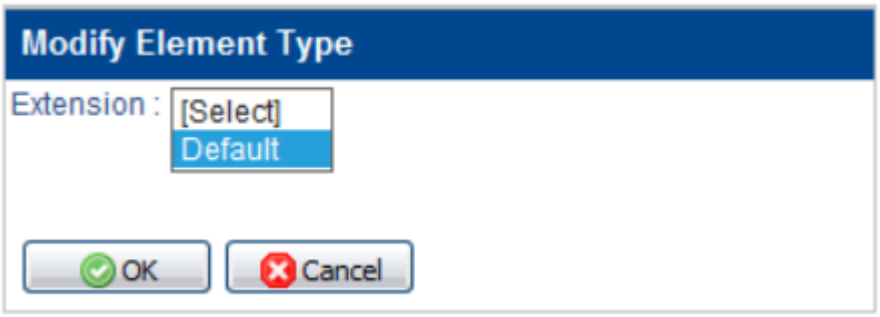


3.6.2 Updates to Tabulations

Prior to creating new tabulations leafs or performing lifecycle operations on existing tabulations leafs, modify the Tabulations folder type.

To modify the Tabulations folder type:

1. Select the greyed **Tabulations** folder and in the **More** drop-down list click **Change Type**.
2. Choose **Default** from the **Extension** list, and then click **OK**.
3. On the warning message that appears (stating that changing the type will erase publishing information), click **OK**.



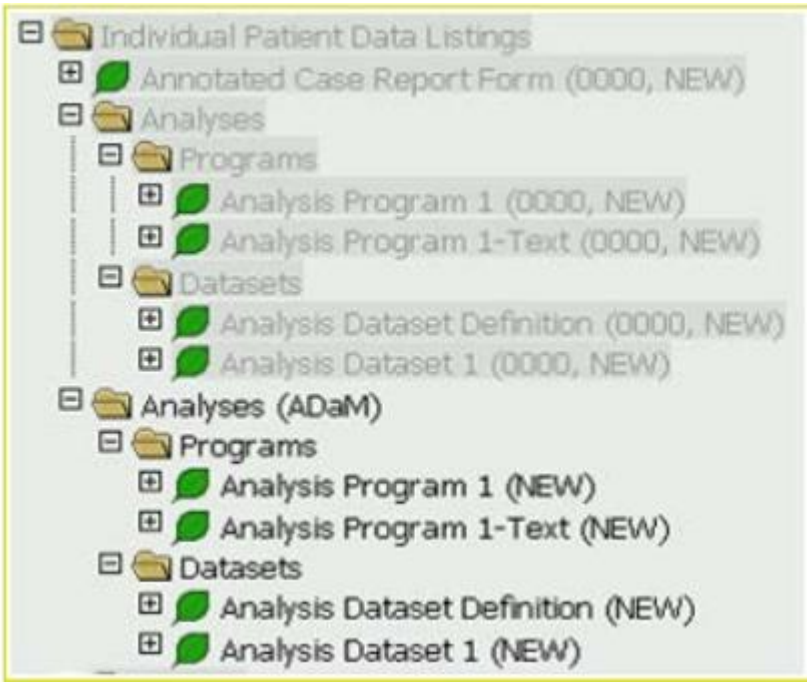
3.6.3 Adding ADaM Datasets to Existing Study

The ADaM structure can live side-by-side with the previous legacy analysis dataset structure.

To add the ADaM dataset structure:

1. Right-click on any folder in the assembly tree and use the **Import Assembly Wizard** to locate the ICH E3 Clinical Study Report (VV3-0, Study Data v2-0) template.

2. Show the template and open the folders to display the structure under Individual Patient Data Listings.
3. Drag the Analyses (ADaM) folder onto the grayed, existing Analyses folder.
4. Promote the Analyses (ADaM) folder to make it a sibling to Analyses.



Note that the Analyses (ADaM) folder has an Output Path set to 'analysis/adam'. The Datasets subfolder has an Output Path set to 'datasets'. This will place the ADaM datasets in the correct folder structure, as shown in the Study Data Specification v2.0.

3.6.4 Adding SEND Datasets to Existing Study

The SEND dataset structure can be added under the existing Tabulations structure.

To add the SEND dataset structure:

1. Right-click on any folder in the assembly tree and use the **Import Assembly Wizard** to locate the ICH E3 Clinical Study Report (VV3-0, Study Data v2-0) template.
2. Show the template and open the folders to display the structure under Individual Patient Data listings/Tabulations.
3. Drag the SEND Datasets folder onto the grayed, existing Tabulations folder so that it becomes a child of Tabulations.

Note that the SEND Datasets folder has an Output Path set to tabulations/send. This will place the SEND datasets in the correct folder structure, as shown in the Study Data Specification v2.0.

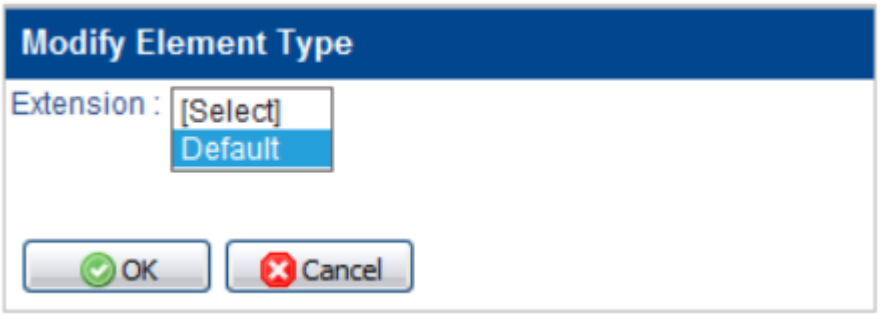
3.7 Lifecycle Operations on Existing Datasets

3.7.1 Analysis Datasets

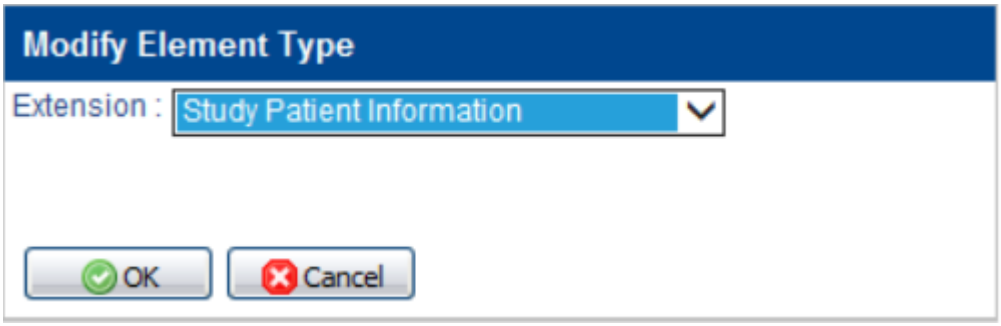
For legacy analysis datasets that have lifecycle operations applied in future sequences, the Analyses folder type must be modified. Perform the lifecycle operations on the analysis dataset leafs as needed.

To modify the Analyses folder type:

1. Select the dimmed Analyses folder and in the **More** drop-down list and click **Change Type**.
2. In the **Extension** list choose Default, and then click **OK**.
3. On the warning message that appears (stating that changing the type will erase publishing information), click **OK**.



4. Repeat the **Change Type** process on the Analyses folder, this time choosing **Study Patient Information** as the Extension, and then click **OK**.



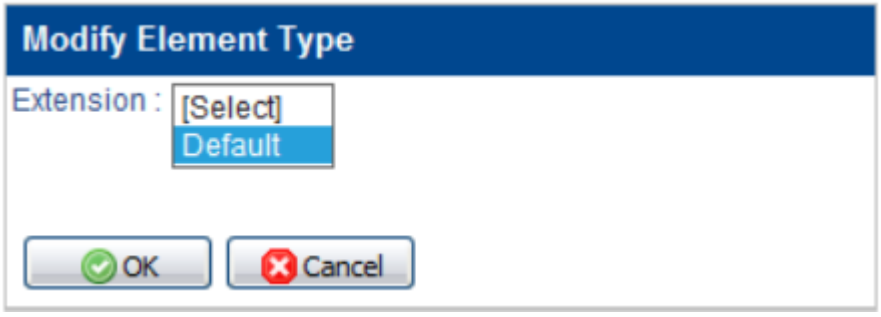
5. Edit the Analyses folder attributes and enter the following fields. (The Site field should be blank.)
    a. **Output Folder** – analysis/legacy
    b. **Subject Matter** – analysis-dataset-legacy

3.7.2 Legacy Tabulations

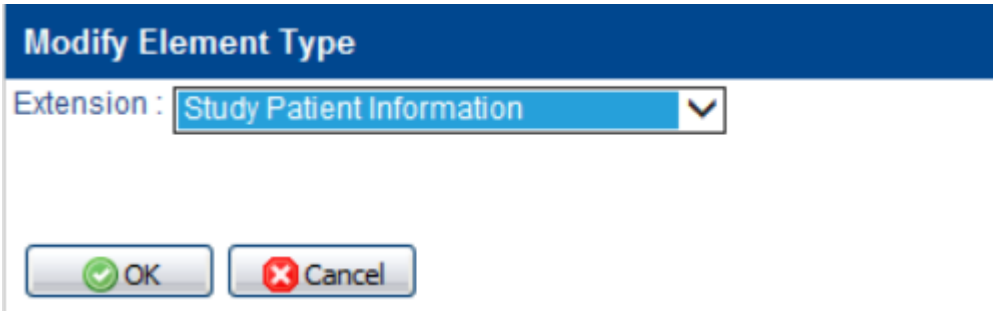
For legacy tabulations that have lifecycle operations applied in future sequences, the Legacy folder type must be modified. Perform the lifecycle operations on the tabulations leafs as needed.

To modify the Legacy folder type:

1. Select the dimmed Legacy folder and in the **More** drop-down list click **Change Type**.
2. In the Extension list choose **Default**, and then click **OK**.
3. On the warning message that appears (stating that changing the type will erase publishing information), click **OK**.



4. Repeat the **Change Type** process on the Legacy folder, this time choosing **Study Patient Information** as the Extension, and then click **OK**.



5. Edit the Legacy folder attributes and enter the following fields. (The Site field should remain blank.)
    a. **Output Folder**: tabulations/legacy

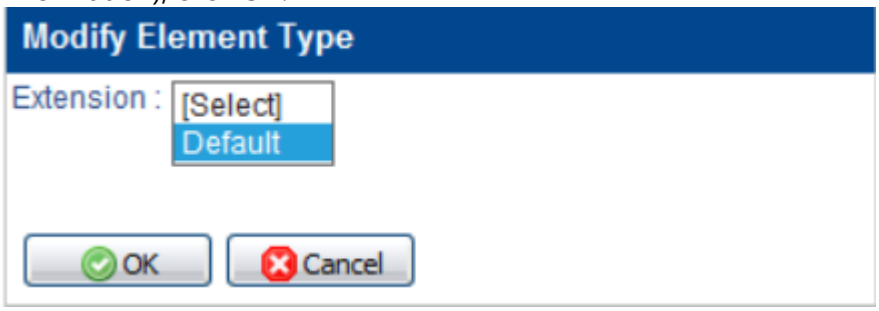
b. **Subject Matter**: data-tabulation-dataset-legacy

3.7.3 SDTM Tabulations

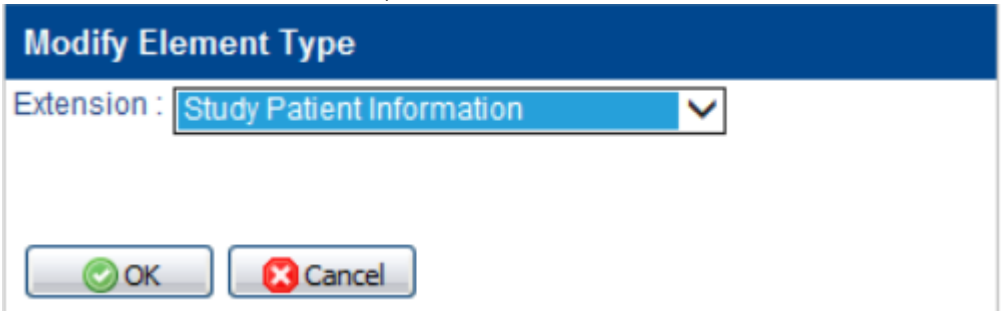
For SDTM tabulations that have lifecycle operations applied in future sequences, the SDTM Datasets folder type must be modified. Perform the lifecycle operations on the tabulations leafs as needed.

To modify SDTM Datasets folder types:

1. Select the greyed SDTM Datasets folder and in the **More** drop-down list click **Change Type**.
2. In the Extension list choose **Default**, and then click **OK**.
3. On the warning message that appears (stating that changing the type will erase publishing information), click **OK**.



4. Repeat the **Change Type** process on the SDTM Datasets folder, this time choosing **Study Patient Information** as the Extension, and then click **OK**.



5. Edit the SDTM Datasets folder attributes and enter the following fields. (The Site field should remain blank.)
   a. **Output Folder**: tabulations/sdtm
   b. **Subject Matter**: data-tabulation-dataset-sdtm