Health Canada Santé Canada

Guidance Document

Preparation of Regulatory Activities in the Electronic Common Technical Document (eCTD) Format

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Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

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Ligne directrice Préparation des activités de réglementation en format Electronic Common Technical Document (eCTD)

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Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent, and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy, or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

REVISION HISTORY

Date	Description
May 17, 2004	Draft Guidance for Industry: Preparation of Drug Submissions in eCTD Format (co-submission filing format only)
May 16, 2005	Guidance for Industry: Preparation of Drug Submissions in eCTD Format (co-submission filing format only)
January 20, 2006	Draft Guidance for Industry: Preparation of Drug Submissions in eCTD Format (co-submission and hybrid filing formats)
September 17, 2008	Guidance for Industry: Preparation of Drug Submissions in eCTD Format (co-submission and hybrid filing formats)
March 30, 2012	Draft Guidance Document: Preparation of Drug Regulatory Activities in eCTD
May 14, 2015	Guidance Document: Preparation of Drug Regulatory Activities in eCTD
February 21, 2020	Guidance Document: Preparation of Regulatory Activities in eCTD Format (Revisions include expansion of eCTD scope, clarification resulting from industry feedback and lessons learned with eCTD format, consolidation of the CTD guidance document and addition of detailed instructions for Master Files)
March 13, 2020	Guidance Document: Preparation of Regulatory Activities in eCTD Format (corrections of footnote errors)

Table of contents

1 INTRODUCTION

1.1 Policy Objectives

To integrate the electronic Common Technical Document (eCTD) format within the Canadian drug registration framework by describing the electronic format requirements for regulatory activities [1] filed pursuant to the Food and Drugs Act and Regulations.

To facilitate the preparation of a regulatory activity for human drugs, pursuant to Part C of the Food and Drug Regulations, in the eCTD format.

1.2 Policy Statements

This guidance document defines the eCTD electronic-only format process requirements and provides guidance on the structure and content of information to be included in regulatory activities filed to Health Canada.

This guidance document is to be used in the preparation and filing of drug regulatory activities to Health Canada in the eCTD electronic-only format as established by the International Council on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. This guidance document reflects recommendations made by the ICH working groups and steering committee, incorporates suggestions made by stakeholders, and describes both new and revised filing requirements.

Some information outlined in this guidance document may not be used with the current Canadian Module 1 schema. Alternative instructions are provided and indicated throughout the document using footnotes.

1.3 Scope and Application

The table below provides a list of the regulatory activity types for human drugs that are mandatory or recommended for filing in the eCTD format.

Table 1: Outline of eCTD Requirement and Regulatory Activity types

eCTD Requirement	Regulatory Activity Type
Mandatory in eCTD format	**Division 8 - Prescription and non-Prescription (Human Drugs only) – including Administrative (i.e. NDS, ANDS) and Labelling ONLY regulatory activities.** • New Drug Submission (NDS) [2] • Supplement to a New Drug Submission (SNDS) [2] • Abbreviated New Drug Submission (ANDS) [2] • Supplement to an Abbreviated New Drug Submission (SANDS) [2] • Extraordinary Use New Drug Submission (EUNDS) [2] • Extraordinary Use Supplement to a New Drug Submission (EUSNDS) [2] • Extraordinary Use Abbreviated New Drug Submission (EUANDS) [2]

[1] See definition in Appendix B.

[2] Including regulatory activities for administrative changes and labelling only.

eCTD Requirement	Regulatory Activity Type

	• Extraordinary Use Supplement to an Abbreviated New Drug Submission (EUSANDS)[2]
	• New Drug Submission for Disinfectant products (NDS-D)[2,3]
	• Supplement to a New Drug Submission for Disinfectant products (SNDS-D)[2,3]
	• Supplement to a New Drug Submission-Confirmatory (SNDS-C)
	• Notifiable Change (NC)[2]
	• Request for Priority Review Status for NDS or SNDS
	• Yearly Biologic Product Report (YBPR)[4]
	• Pre-Submission Meeting Information[5] (MPNDS, MPSNDS, or MPNC)
	• Undefined Regulatory Activity (UDRA)[6] - with the exception of Notification of Discontinued Sale (DIN cancellation) and Notification of interruption of sale
	• Development Safety Update Report (DSUR) when provided as a **standalone** regulatory activity to Therapeutic Products Directorate (TPD), Biologics and Genetic Therapies Directorate (BGTD) or Natural and Non-prescription Health Products Directorate (NNHPD)
	• Periodic Safety Update Report - Confirmatory (PSUR-C) or Periodic Benefit Risk Evaluation Report - Confirmatory (PBRER-C) when provided to TPD, BGTD or NNHPD - submitted to support the fulfilment of a Notice of Compliance with Conditions (NOC/c)
	• Post NOC - Level III Changes Form
	
	Division 8 - Post-market Vigilance Data (Human Drugs only)
	
	• Periodic Safety Update Report (PSUR) or Periodic Benefit Risk Evaluation Report (PBRER) when provided to the Marketed Health Products Directorate (MHPD)
	• Risk Management Plan (RMP), when provided to MHPD
	• Other Post-market Vigilance data (Undefined Data Post-market Vigilance (UDPV)) requested by MHPD
	  ○ Post-Authorization commitments - Post market Vigilance (PA-PV)
	  ○ Post-Authorization Act and Regulations - Post market Vigilance (REG-PV)
	  ○ Issue Related Summary Report (IRSR-PV)
	  ○ Risk Communication - Post market Vigilance (RC-PV)
	  ○ Patient Safety/Advertising Ad-Hoc Post market requests (PSA-PV)

[3] This regulatory activity type (NDS-D, SNDS-D) should be indicated in the cover letter of the transaction, however NDS or SNDS must continue to be used in building the eCTD regulatory transaction as the new regulatory activity types are not in the eCTD Module 1 backbone.

[4] YBPRs should not be filed in the same regulatory transaction with Level III change forms.

[5] Pre-Submission Meeting Information includes the Pre-Submission Meeting Request.

[6] UDRA should be used as per Appendix F of this guidance document.

eCTD Requirement	Regulatory Activity Type
Mandatory in eCTD format as of January 2020	**Master Files*** • New Type I Master Files - Drug Substance • New Type II Master Files - Container Closure Systems and Components • New Type III Master Files – Excipients • New Type IV Master Files - Drug Product * excludes master files for Veterinary Drug Directorate

Recommended in eCTD format	**Division 5 - Clinical Trials (Human Drugs only)**
	• Pre-Clinical Trial Application Consultation Meeting (Pre-CTA)
	• Clinical Trial Application (CTA) with either a 7 day administrative or a 30 day default performance standard
	• Clinical Trial Applications - Amendments (CTA-A) with a 7 day administrative or a 30 day default performance standard
	• Clinical Trial Application-Notification (CTA-N)
	
	Division 1 - Prescription and non-Prescription (Human Drugs only)
	• Application for Drug Identification Number (DINA)
	• Application for Drug Identification Number - Biologic (DINB)
	• Application for Drug Identification Number - Disinfectant (DIND)
	• Application for Drug Identification Number - Category IV Product (DINF)
	• Post-Authorization Division 1 Change (PDC)
	• Post-Authorization Division 1 Change - Biologic (PDC-B)
	• Post-DIN Notification (for DINA only)
	• Yearly Biologic Product Report (YBPR) - Biologic
	• Pre-Submission Meeting Information (MPDIN)
	• Periodic Safety Update Report (PSUR) or Periodic Benefit Risk Evaluation Report (PBRER) when provided to the Marketed Health Products Directorate (MHPD)
	• Risk Management Plan (RMP), when provided to MHPD
	• Other Post-market Vigilance data (Undefined Data Post-market Vigilance (UDPV)) requested by MHPD
	  ○ Post-Authorization commitments - Post market Vigilance (PA-PV)
	  ○ Post-Authorization Act and Regulations - Post market Vigilance (REG-PV)
	  ○ Issue Related Summary Report (IRSR-PV)
	  ○ Risk Communication – Post market Vigilance (RC-PV)
	  ○ Patient Safety/Advertising Ad-Hoc Post market requests (PSA-PV)
	
	Division 8 Prescription and non-Prescription (Human Drugs only)
	• Undefined Regulatory Activity (UDRA)
	  ○ Notification of Discontinued Sale (DIN cancellation)
	  ○ Notification of interruption of sale

eCTD Requirement	Regulatory Activity Type

	Master Files
	• Conversion of existing
	  ○ Type I Master Files - Drug Substance
	  ○ Type II Master Files - Container Closure Systems and Components
	  ○ Type III Master Files - Excipients
	  ○ Type IV Master Files - Drug Product

The eCTD transaction for regulatory activity types listed above that are not currently in the Guidance Document: Creation of the Canadian Module 1 Backbone should be prepared using the example below. Until the backbone document has been updated, or the regulatory activity types are available on the eCTD tools being used by sponsors, sponsors should indicate the correct regulatory activity type on the cover letter of the transaction.

For example:

> **EUANDS** should be indicated on the cover letter; however, the eCTD sequence should be prepared using the **ANDS** regulatory activity type, as the EUANDS option is not available in the ca-regional backbone.
>
> **SNDS-D** should be indicated on the cover letter, however, the eCTD sequence should be prepared using the **SNDS** regulatory activity type as the SNDS-D option may not be available on the eCTD tool as it is not available in the ca-regional backbone.
>
> **PA-PV** should be indicated on the cover letter, however, the eCTD sequence should be prepared using the **UD-PV** regulatory activity type as the PA-PV option may not be available on the eCTD tool as it is not available in the ca-regional backbone.

The eCTD format is mandatory for drug/device combinations where there is a drug review lead (e.g. the product falls under the Food and Drug Regulations) as described in the Drug/Medical Device Combination Products policy on the Health Canada website where the combination product is classified as a device, the use of eCTD format for the drug component is also encouraged.

Transactions, related to a regulatory activity that have previously been filed in eCTD format, are mandatory in eCTD format.

A complete list of regulatory transaction descriptions is available, via the Filing Submissions Electronically information page on the Health Canada website.

If a sponsor is unable to use eCTD format for a regulatory activity that has been identified mandatory in eCTD format, individual requests for an exemption will be considered by Health Canada on a case-by-case basis. These requests should be submitted as per the email template below:

> **To**: hc.ereview.sc@canada.ca.
>
> **Subject**: Mandatory eCTD Format - Exemption
>
> **Email body**:
>
> - Company name:
> - Product name:
> - Regulatory activity type:

- Anticipated date of filing:
- Rationale for the exemption:

The rationale for the exemption must include appropriate justification in order to be accepted.

For example:

- Detailed explanation of the challenges related to submitting in eCTD format specific to the product; or
- Reason(s) the sponsor is unable to file in eCTD format at the anticipated date of filing. This must also include the sponsor's transition plan for submitting subsequent regulatory activities and transactions in eCTD format.

Regulatory activity types that are recommended, but not mandatory, in eCTD format will not require an exemption if they cannot be filed in eCTD format.

Regulatory Transactions out of scope for eCTD format

The information currently not accepted in eCTD format includes:

- Products regulated under the Natural Health Products Regulations
- Site Master Files (submitted to Regulatory Operations and Enforcement Branch)
- Site Reference File (SRF)
- Medical Devices - Licence Application or Amendment (LAp or LAm)
- Lot Release documentation (i.e. group 1a, 1b, 2, 3, 4 fax-backs)
- Consistency Lot Testing Activities[7] (Sample Requests) requested during the pre-market review process by BGTD
- Adverse Reaction Reports
- A response to a request issued under the Access to Information Act (ATIA)
- The Annual Drug Notification Form (ADNF) completed by the sponsor
- New Certificate of Supplementary Protection (CSP) Applications
- CSP related Correspondence
- Court documents (for example statements of claim, notices of application, notices of motion, etc.)
- Pipeline meeting

Health Canada will inform sponsors when additional regulatory activity types will be accepted or required in eCTD format.

1.4 Background

The preparation and filing of a regulatory activity and additional information in eCTD format is mandatory for specified regulatory activity types. Sponsors who file a regulatory activity in eCTD format must comply with the specifications included in this guidance document as well as the following documents available on the Health Canada website:

[7] All requested documentation should be submitted with the requested samples directly to the BGTD. The documentation does not need to be provided again within the eCTD response sequence. The eCTD response sequence should consist of the cover letter, life cycle management table (eCTD), issued clarification request and a response with confirmation that the documentation and samples have been shipped to the BGTD.

- Guidance Document: Creation of the Canadian Module 1 Backbone
- Canadian Module 1 Schema Version 2.2
- Validation Rules for regulatory transactions in eCTD format
- Organization and Document Placement for Canadian Module 1 of the Common Technical Document (CTD) Structure
- Regulatory Transaction Descriptions
- Electronic Common Technical Document Specification (Version 3.2.2, July 16, 2008) including the corresponding Questions and Answers, developed by the ICH M8 Expert Working Group (EWG)

Regulatory transactions in eCTD format that do not comply with the requirements prescribed in this document will be rejected.

Sponsors should also consult other related Health Canada guidance documents and notices as listed in Appendix A of this document.

1.5 Contact Information

Any questions related to this guidance document should be sent via email to hc.ereview.sc@canada.ca.

2. STRUCTURE AND CONTENT

Health Canada's content and document placement requirements for regulatory activities in eCTD format are the same as they are for those filed in the non-eCTD electronic-only format. This guidance document and corresponding ICH guidance documents on the CTD format outline the modular structure and content of regulatory activities in electronic format.

It is necessary to understand the distinction between the folder structure and the eCTD structure.

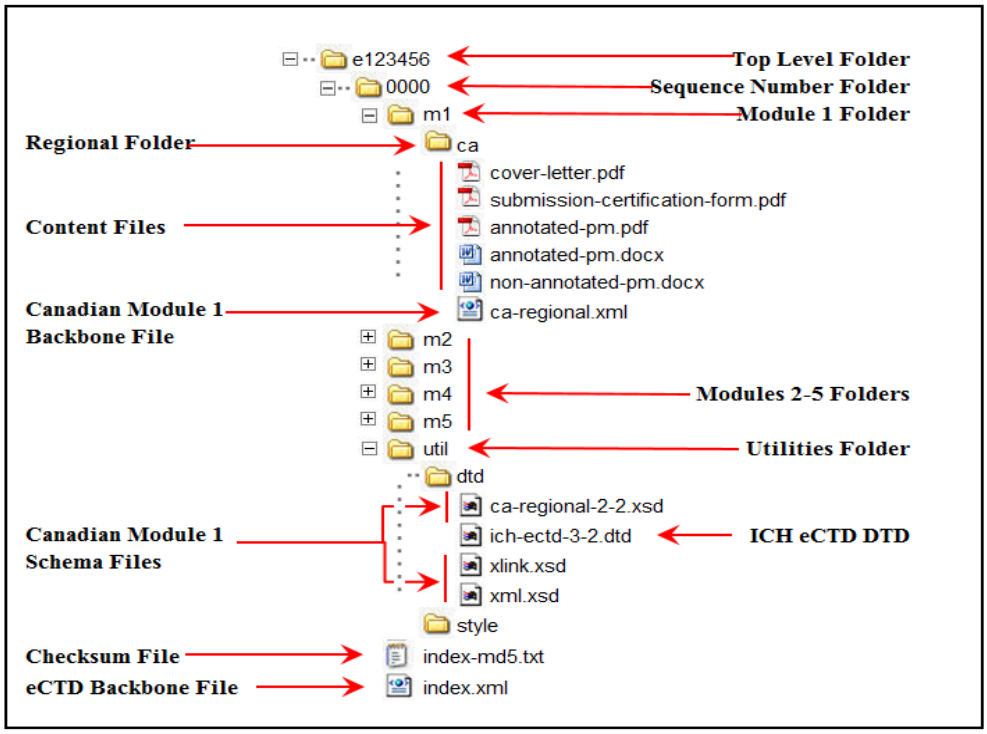
Folder Structure

A folder is the organizing unit for a computer operating system and the unit in which electronic files are stored and accessed on a computer.

Windows Explorer®, for example, provides the means for storing, saving, viewing, and accessing files in folders on a computer using the Windows operating system.

Figure 1 illustrates a portion of the folder structure for storing files in a regulatory activity in eCTD format, as seen using Windows Explorer®.

Figure 1: Folder Structure with one Regulatory Transaction



eCTD Structure

The eCTD structure is the rendering of the regulatory activity through its organization in an eXtensible Markup Language (XML) backbone. The eCTD structure can be viewed by using an XML viewing tool. Figures 2 and 3 illustrate a portion of the eCTD structure, as seen using an XML viewing tool. While Figure 2 illustrates a dossier with one regulatory transaction, Figure 3 illustrates a dossier with multiple regulatory transactions.

Figure 2: eCTD Structure with one Regulatory Transaction

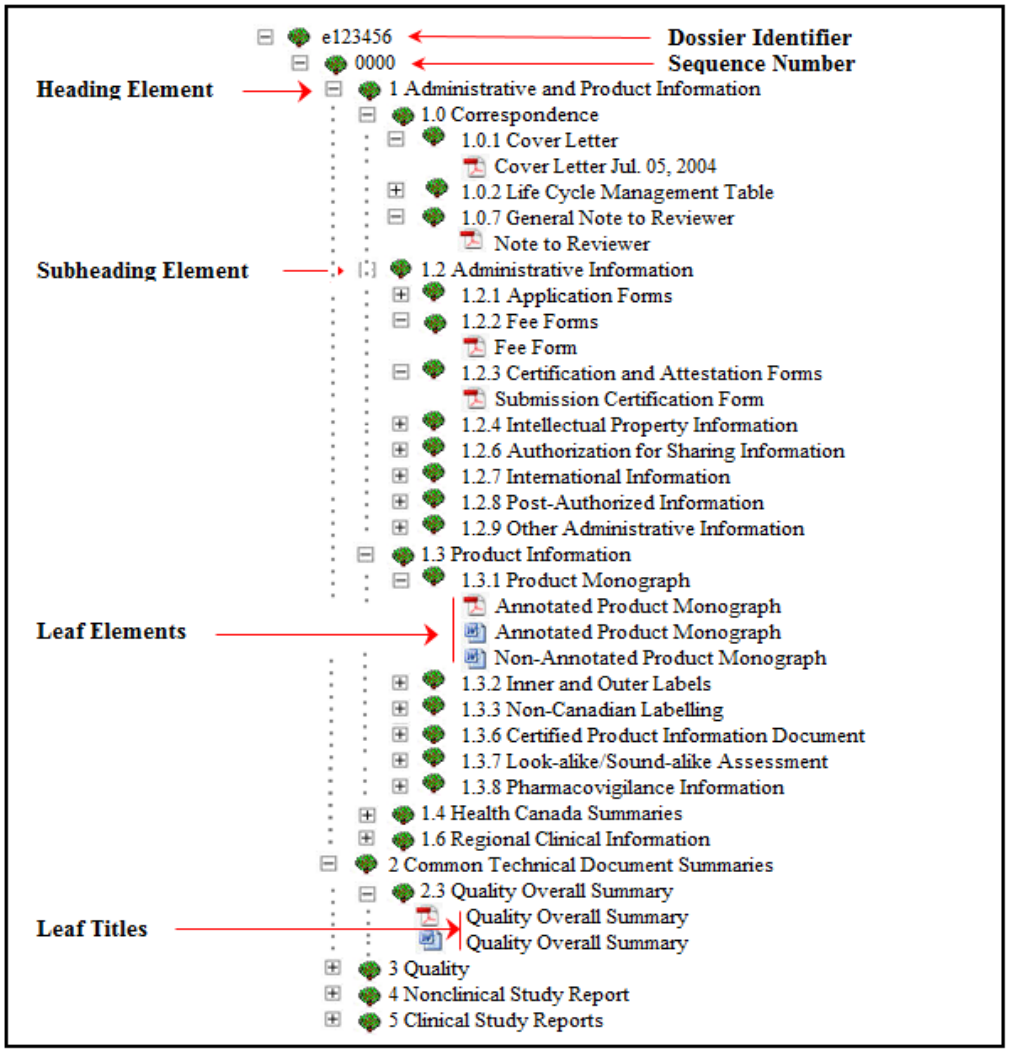
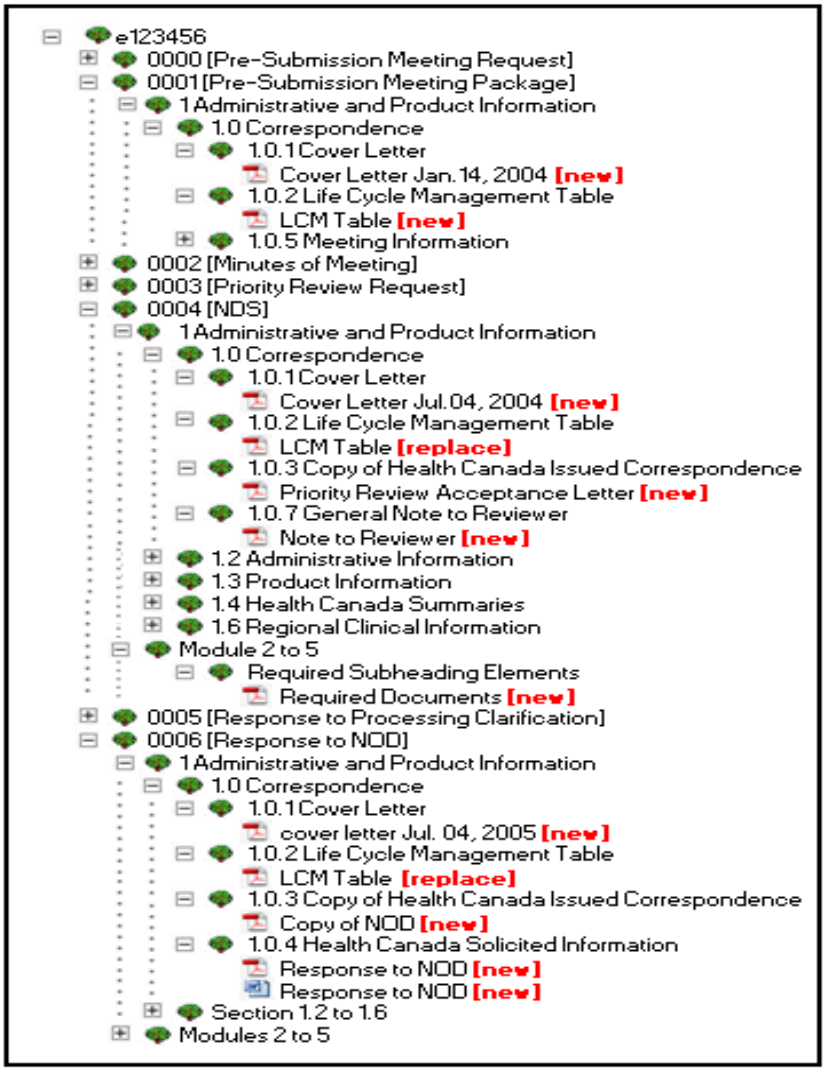


Figure 3: eCTD Structure with Multiple Regulatory Transactions



2.1 Cover Letter

All regulatory transactions in eCTD format **must** be accompanied by an administrative cover letter in electronic portable document format (PDF), with the exception of transactions containing only a Post NOC - Level III Changes Form or Letters of Access (for a Master Files).

All cover letters must be three pages or less in length and only contain a subset of the below prescribed information.

Health Canada requires the following for all cover letters:

- Clearly state what is being provided and the reason for filing as per the Regulatory Transaction Description document
- Indicate the:
  - Stakeholder[8] Name and Role (e.g. Sponsor, Manufacturer, DIN / MF Owner, or Agent)
  - Brand name or Master File (MF) name
  - Control number or MF number (if known)
  - Dossier Identifier
  - Regulatory Activity type
  - Sequence number
- Include reference to a correspondence and/or a request letter issued by Health Canada (including an Advisement Letter), if applicable
- Clearly state any cross-referenced regulatory activity (include the date the regulatory activity was approved)
- Indicate the contact name and email address for the eCTD publisher where the Validation Report (if required) should be sent
- Signature: see section 4.6
- If applicable, include a list of eligible patent claims and a description of how such claims correspond to the regulatory activity in respect of which the patent list is filed, as well as page references to relevant portions of the drug submission should be included
- Include detailed information regarding the following transactions:
  - Other Sale Notifications (SN):
    - Notifications of interruption of sale should indicate the:
      - DIN(s) affected
      - Date the sale of the drug stopped (the cover letter should indicate that the product has not been sold for a period of 12 consecutive months)
    - Notifications of discontinuation of sale (DIN cancellation) should indicate the:
      - DIN(s) to be cancelled
      - Discontinuation date
      - Expiry date of the last lot sold
      - Lot number of the last lot sold
    - Special Requests (DNF)

  - Responses to requests for clarification should clearly indicate the name of the requester.
  - PSUR or PBRER (when provided to MHPD) should also indicate which of the following applies:
    - Significant change in what is known about the risks and benefits of the health product
    - VOLUNTARY PSUR/PBRER - unsolicited information
    - REQUESTED PERIODIC PSUR/PBRER - requested by Health Canada (for example RMP follow-up or post-authorization commitment)

[8] See definition in Appendix B.

- REQUESTED AD HOC PSUR/PBRER - provided as a one-time request made by either the pre-market review directorate reviewing the associated regulatory activity or by MHPD (the requester should be specified)

- RMP (when provided to MHPD) should also indicate which of the following applies:
  - VOLUNTARY RMP - unsolicited information
  - REQUESTED AD HOC RMP - provided as a one-time request made by MHPD (the requester should be specified)

- UD-PV (when provided to MHPD) cover letter should indicate the new regulatory activity type (PA-PV, REG-PV, IRSR-PV, RC-PV or PSA-PV) in lieu of UD-PV
- DINAs should indicate if there is a labelling reference product
- DSUR (when provided to TPD or BGTD) should also indicate which of the following applies:
  - VOLUNTARY - unsolicited information
  - REQUESTED - provided as a response to a request made by Health Canada

- Master File conversion including any new updates or a new Letter of Access (LoA) which has previously not been authorized should be clearly identified

2.2 Life Cycle Management Table

A Life Cycle Management (LCM) Table describes all regulatory transactions and how they relate to each other.

The LCM table is no longer required for transactions submitted to Health Canada. However, if provided, the LCM table should be completed using the example provided in **Appendix C**. When filing a corrected regulatory transaction due to failure of validation, there is no need to update the LCM table.

2.3 Folder Structure and File Naming Convention

For an illustration of the folder structure, see Figure 1.

2.3.1 Top Level Folder and Dossier Identifier

The top level folder of a dossier in eCTD format contains all other folders and the content. The name of the top level folder is the Dossier Identifier number (e.g., e123456, in Figure 1) obtained from Health Canada (refer to Section 4.5, "Request for Dossier Identifier"). This number is the unique identifier for the dossier related to a specific drug product (see appendix C for definition). All subsequent regulatory activities and additional information in eCTD format for the same dossier should retain the same identifier. The top level folder should be included every time a regulatory transaction is provided to Health Canada.

2.3.2 Sequence Number Folder

All files and folders in a regulatory transaction are to be placed under the sequence number folder, as described in the ICH Electronic Common Technical Document Specification (Version 3.2.2), "File Names and Directory Structure," p. 6-1 and 6-2. The sequence number folder should be named using a four-digit number.

The sequence number folder (see Figure 1) includes an m1 subfolder, m2-m5 subfolders (as required), an util subfolder, the eCTD backbone file (index.xml), and the checksum file (index-md5.txt).

The sequence number for the first regulatory transaction for a dossier in eCTD format must be 0000. Each time a sponsor provides new information (a subsequent transaction) for that dossier, the sequence number for that transaction must be the next incremental number, e.g. 0001, 0002.

When resubmitting a corrected regulatory transaction due to a validation error, the sequence number for the transaction should remain the same.

2.3.3 Module 1 Folder

The structure of the Module 1 folder (m1) is defined in Health Canada's Guidance Document: Creation of the Canadian Module 1 Backbone. Sponsors should use the most recent version of the Canadian Module 1 Schema posted on the Health Canada website. The m1 folder contains a ca folder, which contains all Module 1 content files and the Canadian Module 1 Backbone file (ca-regional.xml). The ca folder should not contain any subfolders.

The placement of module 1 documents are defined in the document Organization and Document Placement for Canadian Module 1 of the CTD Structure, available on the Filing Submission Electronically information page.

2.3.4 Modules 2 to 5 Folders

The structure and content of the Modules 2 to 5 folders (m2-m5) are defined in the ICH Electronic Common Technical Document Specification, and other relevant ICH guidance documents listed in Appendix A.

2.3.5 util and dtd Folders

The util folder contains a dtd (document type definition) folder. The dtd folder should contain the Canadian Module 1 Schema file (ca-regional-2-2.xsd), used to define the Canadian Module 1 Backbone, and related files (xlink.xsd and xml.xsd). The dtd folder should also contain the ICH eCTD DTD (ich-ectd-3-2.dtd) used to define the eCTD backbone file (index.xml).

2.3.6 Content File Naming Convention

Choice of file naming convention is up to the sponsor. For easier navigation, a meaningful naming of files that reflect their content should be applied. Not all document e.g. in module 1 should be named Cover letter.

To assist sponsors, this section presents naming convention examples for Module 1 content files. Health Canada suggests that file names begin with the sequence number, followed by the module and the section number, and then a phrase describing the content of the file. All components of the file name should be separated by hyphens.

Meaningful abbreviations, such as PM for Product Monograph, can be used to shorten file names. The following are examples of an optional file naming convention for Module 1:

0000-m107-general-note-to-reviewer.pdf
0000-m131-annotated-pm.pdf
0001-m131-note-to-reviewer-pm.pdf

The file naming convention for files related to the **Public Release of Clinical Information (PRCI)** for Modules 2 to 5 must be named using the suffix "red" added e.g. "study-id-red.pdf".

File names must be limited to a maximum of 64 characters, including the file extension. For further requirements on file extension and name refer to the ICH Electronic Common Technical Document Specification (Version 3.2.2), "File Extension" and "Name", page 2-3.

2.4 eCTD Structure and Leaf Title

For an illustration of the eCTD structure, see Figure 2.

2.4.1 Module 1: Administrative and Product Information

Required documents should be filed as a leaf element under the relevant headings (based on their placement identified in Organization and Document Placement for Canadian Module 1 of the CTD Structure. (i.e. the PDF cover letter leaf element should be placed under the leaf heading: m1-0-1-cover letter).

2.4.2 Modules 2 to 5

If new or updated information is required in response to a clarification request, Screening Deficiency (SDN), Notice of Non-Compliance (NON), Notice of Deficiency (NOD), or other solicited information, then that information should be filed in the same location as the information to which it relates.

For further information about the modified-file attribute used to associate this new or updated information with the information to which it relates, see the ICH Electronic Common Technical Document Specification (Version 3.2.2), "Operation Attribute," pp. 6-3.

The following are a subset of documents and their placement in the eCTD structure, when required:

Applicant's Part (AP) of the Master File (MF)

The Applicant's Part[9] of the MF transactions should be included in section m3-2-s of the eCTD format for a regulatory activity referencing a DMF. When there is more than one MF used for the active substance(s), each MF "Applicant's Part" should be provided in its own m3-2-s section, distinguished by appropriate element attributes.

If the sponsor has their own quality documents that apply to each manufacturer of an active substance(s), in addition to those documents provided by the MF owner, then this information should be placed in a separate m3-2-s section. This section should be identified by appropriate element attributes[10] to distinguish it from the content provided by the MF owner(s).

The figures below are an example of an ANDS that refers to data from two different MF Owners (Company Y Ltd. and Company X Inc.), as well as the data from the sponsor that apply to all manufacturers. When the sponsor incorporates the "Applicant's Part" of the MF into a regulatory activity, there is no need to rename the files that were used in the original MF. These

[9] Also known as "Sponsor's Part".

[10] Since the data provided (such as sponsors' specification) applies to the active substance(s) from all manufacturers, the element attribute should be named "All". This is to consider a situation where a third manufacturer could be added, and the ICH eCTD Specification V 3.2.2 does not allow for the amendment of the element attribute.

repeating m3-2-s sections have been identified by the naming of the folders (see Figure 4) and the element attributes of the eCTD structure (see Figure 5).

Figure 4: Folder Structure for a Master File (MF)

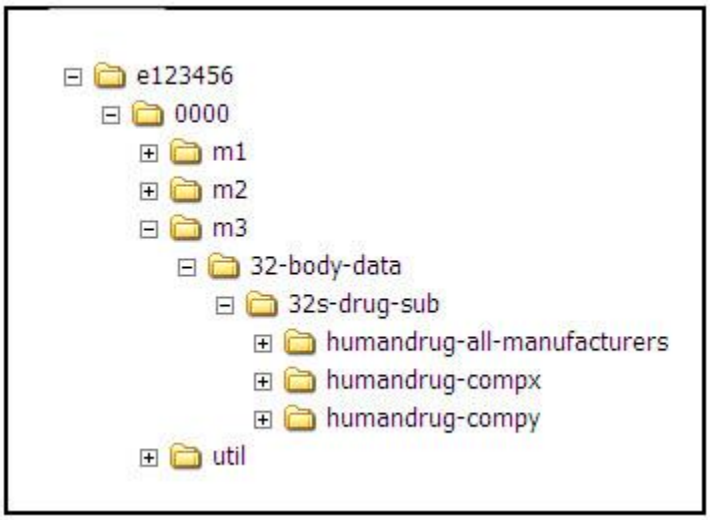
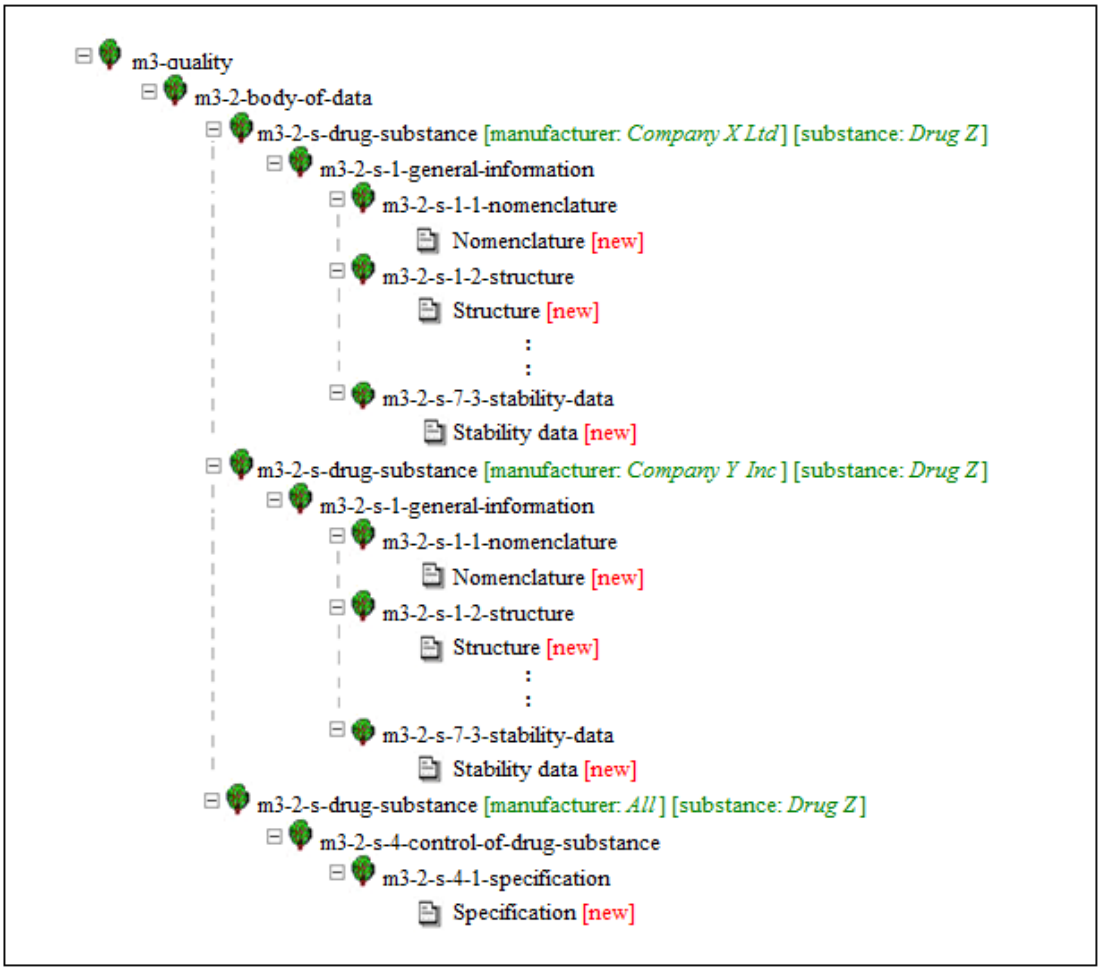


Figure 5: eCTD Structure for a Master File (MF)



Module 3 - 3.2. R Regional Information

To complete the regional section of Module 3, the applicant should refer to the appropriate Health Canada guidance documents. In section 3.2.R, the use of node extension is mandatory. The node extension titles are identified below. If a different title of a node extension was previously used, the same title of the node extension must be used for subsequent information.

- 3.2.R.1 Production Documentation
- 3.2.R.2 Medical Devices
- 3.2.R.3 Lot Release Documentation
- 3.2.R.4 Yearly Biologic Product Report

The Yearly Biologic Product Report (YBPR) and YBPR schedule must be provided in section 3.2.R Regional Information.

The YBPR can be provided as a single document. Alternatively, when the YBPR is provided as multiple documents (YBPR, Analysis of Adverse Drug Reaction, and Recalls) they should be filed as leaf elements under section 3.2.R, and all other documents listed in section 5.1 of the Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs should be filed as leaf elements under the appropriate headings in Module 3.

In both of the cases indicated above, the CPID should be provided as a separate document, filed as a leaf element under the m1-3-6-certified-product-information-document heading.

- 3.2.R.5 Assessment of Similarity
- 3.2.R.6 On Site Evaluation
- 3.2.R.7 Other Regional Information

Module 4 – Nonclinical Study Reports

The applicant should refer to the ICH M4S guidelines, as well as the appropriate Health Canada guidance documents to complete this module.

If provided, Ames reports and Quantitative Structure-Activity Relationship (QSAR) reports must be placed under the Module 4.2.3.7.6 Impurities heading using node extensions or Study Tagging Files (STFs), based on each impurity

Although both node extensions and STFs are acceptable for reports, only one or the other approach should be used consistently throughout the life cycle of the eCTD dossier.

Module 5 – Clinical Study Reports

The applicant should refer to the ICH M4E guideline under Module 5: Clinical Study Reports, and the ICH E3 guideline, Structure and Content of Clinical Study Reports.

- Periodic Safety Update Report (PSUR) or Periodic Benefit Risk Evaluation Report (PBRER)

  The PSUR or PBRER should be filed as a leaf element under the m5-3-6-reports-of-postmarketing-experience heading.

- Case Report Forms (CRFs)

  Case Report Forms (CRFs) and individual patient data listings should be filed as leaf elements under the m5-3-7-case-report-forms-and-individual-patient-listings heading, when provided. According to the ICH Electronic Common Technical Document Specification (Version 3.2.2), “Module 5 Clinical Study Reports”, p. 3-13, the filing of

CRFs within a regulatory activity should be decided on a regional basis. Health Canada prefers that CRFs be organized according to the following principles:

- They should be filed under the m5-3-7-case-report-forms-and-individual-patient-listings heading
- They should be organized first by study "name" then by "site", using node extensions
- Any further breakdown in the organization of CRFs should be developed during discussion with reviewers at the regulatory pre-submission meeting.

Files organized with Study Tagging Files (STFs) will be accepted. If STFs are used in Module 4 and 5, then the CRFs should be built into the STF according to the ICH eCTD STF Specification v2.6.1 and not filed separately under the m5-3-7-case-report-forms-and-individual-patient-listings heading.

Although both node extensions and STFs are acceptable for CRFs, only one or the other approach should be used consistently throughout the life cycle of the dossier in eCTD format.

Study Reports

Study reports should be filed as leaf elements using a node extension under the following headings as applicable:

- m5-3-1-reports-of-biopharmaceutic-studies
- m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials
- m5-3-3-reports-of-human-pharmacokinetic-studies
- m5-3-4-reports-of-humanpharmacodynamic-studies
- m5-3-5-reports-of-efficicacy-and-safety-studies

In order to avoid an inconsistent approach, the files should be organized using node extensions, regardless of whether the study report is broken into multiple files or not.

For new dossiers node extensions must be used in the first regulatory transaction where study reports are provided. For existing dossiers, node extensions must be used with subsequent regulatory transaction where study reports are provided.

Files organized with Study Tagging Files (STFs) instead of node extensions will be accepted. If STFs are used, they should be built according to the ICH eCTD STF Specification v2.6.1.

Although both node extensions and STFs are acceptable for study reports, **only** one or the other approach should be used consistently throughout the life cycle of the dossier in eCTD format.

Documents related to the **Public Release of Clinical Information (**PRCI) must be provided in the original study section (e.g. 5.3.5.1) using a **newly** created STF or node extension.

- The title of the **new** STF/node extension must be same as the one used on the original study with Prefix "RED-*" added for redaction.
- If there was no STF/node extension used with the original study, the **newly** created STF/node extension mustbe named: "RED- StudyID".

Literature References

Literature references should be cited in accordance with the current edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journals Editors (ICMJE).

The literature references (including those related to the PM) should be filed as leaf elements under the following, as appropriate:

- m3-3-literature-references
- m4-3-literature-references
- m5-4-literature-references

2.4.3 Master File Dossiers

Master files are classified according to the various types listed below. There are different content and structural requirements depending on the type of master file that is being filed. For a detailed description of the master file types, refer to the table in section 1.3 "Scope and Application" of the Guidance Document: Master Files (MFs) – Procedures and Administrative Requirements.

Type I – Active Substance Master Files (ASMF)
Type I ASMF contain an "Applicant's Part (AP)" and a "Restricted Part (RP)". The information provided in the MF transaction must be organized as per Appendix E, Table E-1– Distribution of MF Information between the Applicant and Restricted Parts. Refer to Figure E-1 for an example of the eCTD structure.

- **Specifications for Module 2**

  Both Microsoft Word and PDF formats of the Quality Overall Summary (QOS) AP and QOS RP must be included directly under the heading "2.3 Quality Overall Summary", making four leaf elements in total. The leaf titles of the documents must be "QOS (RP)" and a "QOS (AP)". Refer to Figure E-1 for an example of the eCTD structure.

- **Specifications for Module 3**
  The use of attributes for Module 3 (e.g. [substance], [manufacturer]) is mandatory for type I MFs. These attributes must not be changed during the life cycle of the dossier. It is not acceptable to update attributes that are already defined, for example: adding grade (USP) to the [substance: Acetaminophen] attribute field or "Inc" to the [manufacturer: Company X] attribute field.

  The section "3.2.S Drug Substance" should be duplicated and identified as either "AP" or "RP". The section "3.2.A Appendices" will be considered as the Restricted Part (RP). Refer to Figure E-1 for an example on the eCTD structure.

  3.2. Body of Data
  3.2.S Drug Substance [substance: AP-medicinal ingredient] [manufacturer: Company X]
  3.2.S Drug Substance [substance: RP-medicinal ingredient] [manufacturer: Company X]
  3.2.A Appendices
  3.2.A.1 Facilities and Equipment [manufacturer: Company X]
  3.2.A.2 Adventitious Agents Safety Evaluation [manufacturer: Company X]

Type II – Container Closure System (CCS) Master Files and/or Container Closure Components (CCC) Master Files

New Type II Master File (MF) regulatory transactions should be filed in eCTD format using the guidance provided in this document.

The illustrative examples in Appendix E Type II Master Files explain how the current eCTD format, which was not originally designed specifically for master file applications, can be used to organize information related to the container closure component(s) and/or container closure system(s) in a master file transaction. The format that should be used to organize information depends on the complexity of the master file content, the amount of information, and the type of information provided. Previously filed master files in the eCTD format **should not** be reformatted retrospectively in accordance with this guidance and the illustrative examples provided.

Refer to scientific guidance documents listed in Appendix A: Reference Documents regarding the scope and extent of information that should be provided for each master file. Please consult with Health Canada if additional guidance is needed, or if an eCTD (v.3.2.2) structural change needs to be made to a previously registered Type II – CCS MF prior to filing your master file update.

- **Specifications for Module 3**

  A Type II MF should be used for filing information on a container closure component (CCC) or a CCC family (i.e., multiple similar types of CCCs) such as:

  - different sizes of the same type of vials;
  - different formulations and/or colours of rubber stoppers;
  - the identical type of aluminum foil used in different container closure systems (or applications) such as blister packs and child resistant plastic bottles; and
  - when the sterilization process of the CCC is being provided.

  And/or a Container Closure System (CCS) such as a:

  - disposable syringe (CCS) consisting of multiple different (CCC) parts: plunger stopper, syringe barrel, plunger rod, flange extender, needle, and needle shield;
  - glass vial consisting of a rubber stopper, crimping ring and plastic cap; and
  - spray pump consisting of a pump and actuator.

  The information on **a container closure component(s) (**CCC) may be provided using option "a" **or** "b" from the following: (**choose one option only**):

  a. the 3.2.S Drug Substance structure (in lieu of the "Drug Substance" per se in the context of using the ICH eCTD structure for filing a Type II Master File); **OR**
  b. the 3.2.P Drug Product structure (in lieu of the "Drug Product" per se in the context of using the ICH eCTD structure for filing a Type II Master File).

  The information for each **container closure system** (CCS) should be provided using a separate 3.2.P Drug Product section and structure (in lieu of a "Drug Product" per se in the context of using the ICH eCTD structure for filing a Type II MF).

  Regardless of which Module 3.2 format is used, relevant information should be entered for all designated eCTD attributes, of which there are:

- two at the 3.2.S level: [substance] and [manufacturer]; AND
- three at the 3.2.P level: [product-Name], [dosageform], and [manufacturer].

The information entered for the attributes should clearly identify the content of each 3.2.S OR 3.2.P section. This is particularly important when more than one 3.2.S OR 3.2.P section is presented within the same Type II – CCS MF. The attributes cannot be easily revised once they are established.

Accordingly, for the:

3.2.S [substance] OR 3.2.P [product-name] attribute:

- enter the CCC, CCC family or CCS name in the applicable field. For life cycle management reasons, it is recommended that a general name be entered.

3.2.P [dosageform] attribute:

- since the [dosageform] attribute name is irrelevant in the context of a Type II Master File, in the majority of cases, it is recommended that [NA] (meaning "Not Applicable") be entered in this field. However, in a case where there are multiple P sections for similar types of CCCs within the same Master File, it is possible for example, to enter the material of construction in the [dosageform] attribute field. In this case, the descriptor should be unique and clearly distinguish the two P sections, along with the [product-name] and [manufacturer] attribute field entries.

3.2.S OR 3.2.P [manufacturer] attribute:

- enter the name of the Manufacturer in this field. For a master file containing (mostly) common information for multiple (similar) types of container closure component(s) (i.e., a family of CCCs), the relevant 3.2.S OR 3.2.P subsections should be used to contain information that is common to all CCCs. Separate subfolders (i.e., one level of node extensions) under either "3.2.S.6 Container Closure System" OR "3.2.P.7 Container Closure System" should be created for information (i.e., documents) that is specific to each CCC (e.g., different formulations, colors, or applications of a CCC).

The information (i.e., documents) on a CCS should be provided in the relevant 3.2.P subsections (instead of under 3.2.P.7 Container Closure System). The packaging information for the CCS should be provided in 3.2.P.7 section.

Information not critical for the quality of the CCC or CCS does not need to be included in the MF (e.g., packaging information for a non-sterile component which is processed further, or the non-product contact CCCs such as the crimping ring and plastic cap of a vial and stopper CCS). Sections that are not applicable or which contain no information should not be included in the master file.

All document titles should clearly identify the content of each document. If necessary, documents can be further organized within a folder using an alpha-numerical system within the document titles which can put multiple documents in a chronological order or grouping.

If necessary, a "Note to the Reviewer" (Module 1.0.7) can be included in the MF to further explain how the information has been organized within each 3.2.S OR 3.2.P section.

Type III – Excipient Master Files (MFs)

New Type III Excipient MF regulatory transactions should be filed using the most appropriate eCTD format in each case, following the guidance provided below and the illustrative examples provided in Appendix E Type III Excipient Master Files. The examples illustrate how the current eCTD format, which was not originally designed for Master File transactions, can be used to organize information related to the excipient(s). The format that should be used to organize the information depends on the complexity of the Master File content, the amount of information, and the type of information provided. Previously registered Master Files in the eCTD format, including eCTD-formatted Type I MFs for excipients, should not be reformatted retrospectively in accordance with this guidance and the illustrative examples provided. Refer to scientific guidance listed in Appendix A: Reference Documents regarding the scope and extent of information that should be provided for each Master File. Consult with Health Canada if additional guidance is needed or if an eCTD (v.3.2.2) structural change needs to be made to a previously registered Type III Master File prior to filing your Master File update.

- **Specifications for Module 3**
  A Type III Master File should be used for providing information on:
    - a single ingredient excipient or a family of similar single ingredient excipients (i.e., multiple similar types of single ingredient excipients); **OR**
    - excipient(s) containing multiple ingredients (e.g., cell culture media added during the formulation of a vaccine) or more complex type III master files containing additional manufacturing information (e.g., coating, gelatin capsules or a sterilization process); **OR**
    - excipients with a substantial amount of information (e.g., a novel excipient, or an excipient of biological origin).

  Depending on the type(s) of excipient(s) and the extent of the information, the MF may be submitted using either:

  a) a separate 3.2.S Drug Substance structure (in lieu of the "Drug Substance" per se in the context of using the ICH eCTD structure for filing a Type III Master File); **and/or**
  b) a separate 3.2.P Drug Product structure (in lieu of the "Drug Product" per se in the context of using the ICH eCTD structure for filing a Type III Master File).

  Regardless of which Module 3.2 format is used, relevant information should be entered for all designated eCTD attributes, of which there are:

    - two at the 3.2.S level: [substance] and [manufacturer]; AND
    - three at the 3.2.P level: [product-name], [dosageform], and [manufacturer].

  The information entered for the attributes should clearly identify the 3.2.S OR 3.2.P content. This is important particularly when more than one 3.2.S OR 3.2.P section is presented within the same Type III Master File. The attributes cannot be easily revised once they are established.

  Accordingly, for the:

    - 3.2.S [substance] OR 3.2.P [product-name] attribute: Enter the excipient name in this field. It is recommended for life cycle management reasons that a general name be entered.
    - 3.2.P [dosageform] attribute: It is recommended that the actual dosage form of the excipient (if applicable) or [NA] (meaning "Not Applicable") be entered in this field.

- 3.2.S OR 3.2.P [manufacturer] attribute: Enter the name of the Manufacturer in this field.

For each excipient containing multiple ingredients, and for each more complex excipient containing, for example, additional manufacturing information, the information should be provided in a separate 3.2.P Drug Product section. The Description and Composition of a multi-ingredient excipient should be provided in 3.2.P.1 (in lieu of the "Description and Composition of the Drug Product" in the context of this application). The description and flow diagram(s) of the manufacturing process used to make the multi-ingredient excipient (e.g., coating, gelatin capsules), or the sterilization process, should be provided in 3.2.P.3.3, if applicable. The information on each ingredient of the excipient (instead of on the "Control of each excipient" in this context), should be provided in a separate 3.2.P.4 subsection, which must also include the name of the ingredient in the [excipient] attribute field, to identify clearly and uniquely each ingredient.

Similarly, if a single 3.2.P section is used to present the information on several single ingredient excipients and/or excipient families, the 3.2.P.4 subsection should be repeated for each excipient and/or excipient family and these should be identified clearly and uniquely using the [excipient] attribute field.

The information regarding the control of the excipient, either containing one ingredient or the mixture of ingredients, should be provided in 3.2.P.5 (in lieu of information on the "Control of the Drug product" in this context).

For excipients with a substantial amount of information (e.g., a novel excipient, or an excipient of biological origin), use of both 3.2.S Drug Substance and/or 3.2.P Drug Product sections might be necessary to organize all of the excipient information.

Sections that are not applicable, or which contain no information, should not be included in the Master File.

All document titles should clearly identify the content of each document. If necessary, documents can be further organized within a folder using an alpha-numerical system within the document titles which can put multiple documents in a chronological order or grouping.

If necessary, a "Note to the Reviewer" (1.0.7) can be included in the MF to explain how the information has been organized within each 3.2.S Drug Substance and/or 3.2.P Drug Product.

- **Specifications for Module 4**

  Toxicology documents included in the MF transaction should be placed as leaf elements in the respective sections of the module 4 folder.

Type IV – Dosage Form and Drug Product Master Files

Type IV MFs contain an Applicant's Part (AP) and a Restricted Part (RP). The information provided in the MF transaction must be organized as per Appendix E, Table E-2 – Distribution of MF Information between the Applicant and Restricted Parts. Refer to Figure E-20 for an example of the eCTD structure.

- **Specifications for Module 2**

  Both Microsoft Word and PDF formats of the Quality Overall Summary (QOS) AP and QOS RP must be included directly under the heading "2.3 Quality Overall Summary", making four

leaf elements in total. The leaf titles of the documents must be "QOS (RP)" and a "QOS (AP)". Refer to Figure E-20 for an example of the eCTD structure.

- **Specifications for Module 3**

  The use of attributes for module 3 (e.g. [product-name], [dosageform], [manufacturer]) is mandatory for type IV MFs. These attributes must not be changed during the life cycle of the dossier. It is not acceptable to update attributes that are already defined, for example: changing the product name from [product-name: productX] to [product-name: productY]; or adding "Inc" to the [manufacturer: Company X] attribute field.

  The section "3.2.P Drug Product" should be duplicated and identified as either "AP" or "RP". The section "3.2.A Appendices" and "3.2.R Regional Information" will be considered as the Restricted Part (RP). Refer to Figure E-20 for an example on the eCTD structure.

  3.2. Body of Data

  - 3.2.P Drug Product [product-name: AP-drug product name][dosageform: Capsule] [manufacturer: Company X]
  - 3.2.P Drug Product [product-name: RP-drug product name][dosageform: Capsule] [manufacturer: Company X]

  3.2.A Appendices

  - 3.2.A.1 Facilities and Equipment [manufacturer: Company X]
  - 3.2.A.2 Adventitious Agents Safety Evaluation [manufacturer: Company X]

  3.2.R Regional Information

  - 3.2.R.1 Production documentation

2.4.4 Leaf Titles

Leaf titles should describe the content of the document in a meaningful way and should not be too lengthy to ensure proper display of the Table of Contents. Meaningful abbreviations, such as PM for Product Monograph, LOA for Letter of Access, and CEP for Certificate of Suitability can be used.

The leaf title of the Request for Clarification should be:

> Request for Clarification dated mmm. dd, yyyy
> (e.g., Request for Clarification dated Jul. 05, 2004)

The format for the date is as outlined in Health Canada's Guidance Document: Creation of the Canadian Module 1 Backbone.

The leaf title of the Post NOC Changes: Level III Form should be:

> Level III Changes yyyy (year filed)

The file extension is an attribute of the file that will appear in the viewing tool. Health Canada's eCTD viewing tool displays icons that differentiate between PDF and Microsoft Word documents, therefore sponsors should not specify the format of a document in the title of the leaf.

> **Incorrect**: Annotated Product Monograph MS Word
> **Correct**: Annotated Product Monograph

Incorrect: Certified Product Information Document PDF
Correct: Certified Product Information Document

Sponsors should not include the numbering of the heading in the title of the leaf, because this is redundant and confusing for the reviewer (See Figure 2 for an example).

Incorrect:

1.3.1 Product Monograph
1.3.1 Annotated Product Monograph

Correct:

1.3.1 Product Monograph
Annotated Product Monograph

Master Files (MF) - In addition to the general requirement for leaf titles, Master files (MF) have specific requirements. For example the leaf title for:

Letter of Access (LOA) – must include the name of the company that access is granted to

Incorrect: LOA
Correct: LOA – Company name

Quality Overall Summary – must include AP and RP in the leaf titles.

Incorrect: QOS
Correct: RP-QOS and AP-QOS.

Comparison document (Side by Side comparison, or Summary of changes)

Incorrect: General Note to Reviewer
Correct: Side by Side Comparison Document

Public Release of Clinical Information (PRCI) have specific requirements for the naming of the leaf titles in Module 2. Leaf titles related to documents for PRCI must use the prefix "RED" in the leaf title, e.g. "RED-Clinical Overview"

3. TECHNICAL REQUIREMENTS FOR REGULATORY ACTIVITIES

3.1 File Formats

The ICH Specification for Submission Formats for eCTD (SSF) (version 1.2) outlines the required file formats of documents submitted for regulatory transactions in eCTD format.

- As per the section 2.2 "Version" of the SSF document, currently recommended versions of PDF are listed on the ICH website (see http://estri.ich.org/recommendations/ for details). Health Canada accepts PDF files saved as PDF version 1.4 through 1.7, PDF/A-1 and PDF/A-2.
- As per the sections 2.8 "Source of Electronic Document," and 2.9 and "Recommendations for Creating PDF Documents and Images," of the SSF PDF versions of documents should be generated from electronic source documents and not from scanned material, except when the source electronic files are not available or when a signature is required.

Note: The Health Canada Validation Rules for regulatory transactions filed in eCTD format found on the Filing Submissions Electronically outline criteria for validating pdf files.

Health Canada requires that sponsors also provide versions of specific documents in their original Microsoft® Word 2010 (.docx) or 2016 (.docx) formats. Note that the required hyperlinks to related information should be included only in the PDF version of files.

Specific format requirements

The documents in Table 2 must be provided in format(s) specified in that table. When PDF **and** Word are selected, the document must be provided in both formats. When a sponsor provides both PDF and Microsoft® Word files of the same document, the leaf elements pointing to these files should be included under the same heading. See Figure 2 for an illustration.

Table 2: Specific format requirements

List of Documents		File Format	
		PDF	Word
Certified Product Information Document (CPID)	Annotated	√	-
	Non-annotated	-	√
Comprehensive Summary: Bioequivalence		√	√
Dear Healthcare Professional Letter		√	√
Fee Form		√	-
HC-SC3011 Form		√	-
Label Safety Assessment Update - Sponsor Attestation		√	√
Product Monograph (PM)	Annotated	√	√
	Non-annotated	-	√
	Second language	√	-
PSEAT-CTA		-	√
Public Communication		√	√
Quality Overall Summary (QOS)	Clinical Trial Applications	-	√
	All other regulatory activities	√	√
Responses to clarification requests for: SDN, NON, NOD or NOC/c-QN		√	√
Sponsor Attestation Checklist for ANDS		√	√
Summary Basis of Decision	Clean	√	-
	Annotated (redlined)	-	√
('√' = Required / '-' = Not Applicable)			

- When providing presentations for meetings with Health Canada (e.g., pre-submission meetings), Microsoft® PowerPoint 2010 (.pptx) and 2016 (.pptx) are acceptable file formats.
- The "BE data sets" must be provided in ASCII format. For more information see Health Canada's Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format, Appendix B: "Computer Format for the Submission of Data for Comparative Bioavailability Studies".
- For **Public Release of Clinical Information (PRCI)** the "Proposed redaction control sheet", information must be provided in .xlsx format.
- Sponsors filing transactions using the Regulatory Enrolment Process (REP) must provide information using the REP XML files instead of the PDF HC-SC3011 Form and the PDF Fee Form.

For information on other acceptable other file formats, contact Health Canada at hc.ereview.sc@canada.ca.

3.2 Transmission of Electronic Data

Common Electronic Submissions Gateway (CESG)

All regulatory transactions in eCTD format must be sent via the CESG, with the exception of those exceeding 10 gigabytes (GB) in size (size of the compressed file that is being sent).

Prior to using the CESG for sending transactions, sponsors must register as a trading partner. For detailed information on how to become trading partner, refer to the CESG information page and the Food and Drug Administration (FDA) User Guide.

Transactions sent to Health Canada require a top level folder to be included, which contains the sequence folder. Refer to Frequently Asked Questions - Common Electronic Submissions Gateway - Question 10 and Figure 5 on the required folder structure.

Note that the requirement to send a test transaction as part of becoming a trading partner is separate from the test transaction required for eCTD validation and evaluation as per the section 4.1 of this guidance document.

Media

The following media formats are acceptable for eCTD transactions greater than 10 GB:

- Universal Serial Bus (USB) 2.0 or 3.0 drive
- Portable External Hard Drive with USB 2.0 or 3.0 interfaces

Contact Health Canada at hc.ereview.sc@canada.ca for other media formats that may be acceptable at the time of filing.

Subsequent to transferring data to a drive, stakeholders should revalidate the regulatory transaction.

A paper copy of the cover letter must accompany the media (unless otherwise indicated), and a pre-paid envelope must be provided if the media is to be returned.

The complete regulatory transaction must be provided on a single drive.

The label on the drive should contain the following information:

- Stakeholder[11] Name
- Brand Name
- Dossier Identifier (Dossier ID)
- Sequence (regulatory transaction) number

Media must be mailed to Health Canada at the address below:

Health Canada
Finance Building
101 Tunney's Pasture Driveway
Address Locator: 0201A1
Ottawa, Ontario
K1A 0K9

[11] See definition in Appendix B.

3.3 Life Cycle Management

When dealing with a regulatory activity in eCTD format, it is important for Health Canada to be able to establish the position of that regulatory activity in relation to the life cycle of its dossier. The following sections outline Health Canada's recommendations regarding handling the life cycle at the dossier, regulatory activity and document layer.

For additional information on life cycle management, see the ICH Electronic Common Technical Document Specification (Version 3.2.2), "Life Cycle Management", pp. 6-2 and 6-3.

3.3.1 Life Cycle Management at the Dossier Layer

The Dossier Identifier links all regulatory activities to the original regulatory activity of a dossier.

Figure 6 illustrates how various types of regulatory activities are linked by the Dossier Identifier.

Figure 6: Regulatory Activities Linked by Dossier Identifier for human drugs

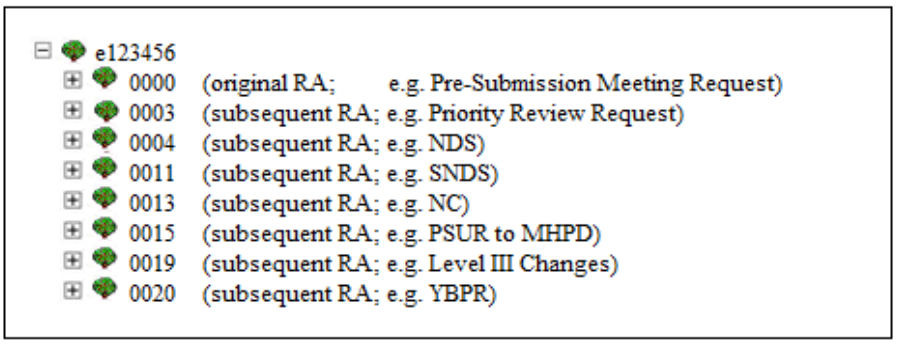
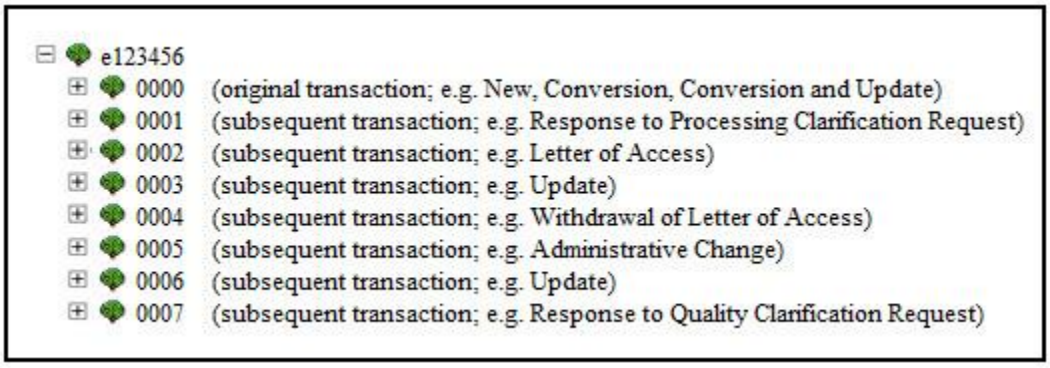


Figure 7 illustrates how various types of regulatory transactions are linked by the Dossier Identifier for Master Files.

Figure 7: Regulatory Transactions Linked by Dossier Identifier for a Master File



3.3.2 Life Cycle Management at the Regulatory Activity Layer

The related-sequence-number element describes the relationship of additional information to the original or a subsequent regulatory activity. For life cycle management at the regulatory activity layer, the related-sequence-number element should be treated as described below:

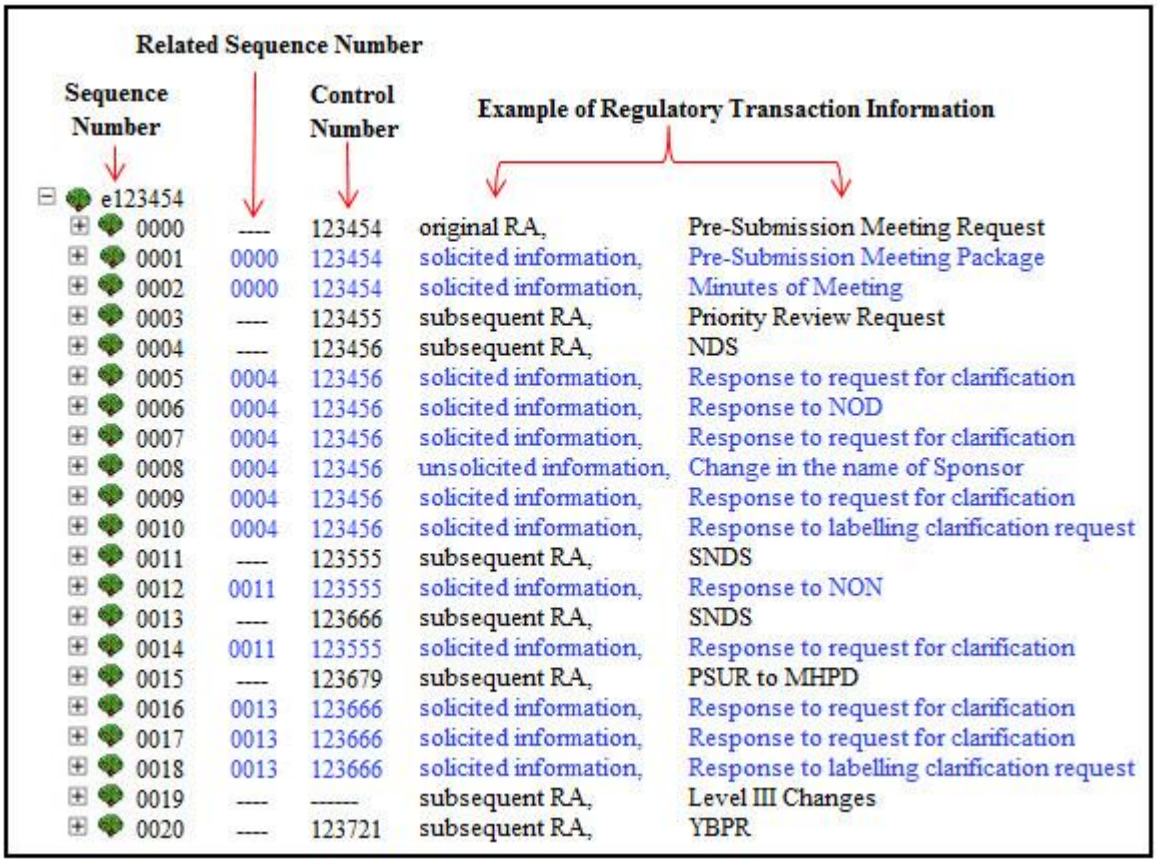
- The first transaction of a regulatory activity (such as NDS, SNDS, including administrative regulatory activities) **should not** be assigned a related-sequence-

number element. (Refer to the related sequence number column in figure 8 below).

- All subsequent transactions of a specific regulatory activity should have the sequence number of the first transaction for that regulatory activity assigned as the related-sequence-number element. The related-sequence-number element must only be one sequence number.
- Exception: transactions related to a regulatory activity that were not previously provided in eCTD format will not have a related-sequence-number element.

Figure 8 illustrates how the related-sequence-number is used to describe the relationship of additional information to the original and subsequent regulatory activities.

Figure 8: Additional information Linked to Regulatory Activities by Related Sequence Number



Sequence Number	Related Sequence Number	Control Number	Example of Regulatory Transaction Information	
e123454				
0000	----	123454	original RA,	Pre-Submission Meeting Request
0001	0000	123454	solicited information,	Pre-Submission Meeting Package
0002	0000	123454	solicited information,	Minutes of Meeting
0003	----	123455	subsequent RA,	Priority Review Request
0004	----	123456	subsequent RA,	NDS
0005	0004	123456	solicited information,	Response to request for clarification
0006	0004	123456	solicited information,	Response to NOD
0007	0004	123456	solicited information,	Response to request for clarification
0008	0004	123456	unsolicited information,	Change in the name of Sponsor
0009	0004	123456	solicited information,	Response to request for clarification
0010	0004	123456	solicited information,	Response to labelling clarification request
0011	----	123555	subsequent RA,	SNDS
0012	0011	123555	solicited information,	Response to NON
0013	----	123666	subsequent RA,	SNDS
0014	0011	123555	solicited information,	Response to request for clarification
0015	----	123679	subsequent RA,	PSUR to MHPD
0016	0013	123666	solicited information,	Response to request for clarification
0017	0013	123666	solicited information,	Response to request for clarification
0018	0013	123666	solicited information,	Response to labelling clarification request
0019	----	------	subsequent RA,	Level III Changes
0020	----	123721	subsequent RA,	YBPR

3.3.3 Life Cycle Management at the Document Layer

The granularity of the document goes hand in hand with life cycle management. Adequate life cycle management is difficult without proper granularity at the document layer.

The operation attribute of the leaf element describes the relationship of content files within the dossier. See Figure 9 for an illustration.

The operation attributes used to manage the life cycle of Word documents should be the same as the attributes used to describe their counterparts in PDF, if applicable.

General Rules for Use of "Append" and "Replace" Operation Attributes:

In general, the use of the operation attributes "replace" and "append" are related to the way the content of a document is managed.

- "Replace" should be used when the additional information and the previously filed information are provided as a consolidated document.
- "Append" should be used when the additional information provided is used to build upon previously filed information, without providing it again.

For example, in subheading elements 3.2.S.7 and 3.2.P.8.3, Stability Data, a document containing stability data for one year is included in sequence 0000, and then updated the following year with the filing in sequence 0001.

In this case, two options are possible when filing transaction 0001. The first option is to create a new document that includes the first year of data plus the additional year of data. In this instance, the operation attribute should be "replace". The second option is to create a new document that includes only the additional year of data. In this instance, the operation attribute should be "append".

The "append" operation attribute **should not** be used in the following cases:

- To link files that have been split due to the 150 megabyte limit. Proper file management, using an adequate level of granularity, should be used instead to ensure no files exceed the size limit.
- To modify a document twice in the same regulatory transaction. Proper file management should be used instead to consolidate or modify the document itself.
- For Module 1 documents.

For an illustration of the general rules, see figures in Appendix D.

General Rules for Use of the "Delete" Operation Attribute

In general, documents provided as "**new**" can be deleted using the "delete" operation attribute at any point, if the document is no longer relevant or required as part of the dossier.

Rules for Use of Operation Attributes for Specific Documents

The operation attribute for the life cycle management at the document layer for specific documents should be treated as described below. For further information, see the ICH Electronic Common Technical Document Specification (Version 3.2.2), "Operation Attribute" p. 6-3.

The operation attribute for the leaf element(s) of the following documents should **always** be "**new**":

- All content files provided for the first time as part of the any regulatory activity
- Cover letter
- Note(s) to reviewer
- Level III Changes Form
- PSUR or PBRER when provided to MHPD[12]
- RMP when provided to MHPD
- A copy of the original request from Health Canada

[12] PSUR and PBRR are provided for a specific period therefore, never replacing the previous document.

- The summary of responses to a request in a question and answer format
- Side by side comparison document
- Summary of Changes
- Yearly Biologic Product Report (YBPR)
- Patent Form IVs
- Patent Form Vs
- MF Application Fee Form

The operation attribute for the leaf element(s) of the following documents should be "**new"** when provided for the first time, and "**replace**" whenever provided again with amendments as part of a subsequent transaction:

- The Life Cycle Management (LCM) Table
- Certification of Suitability (CEP)[13],
- BSE / TSE Attestation Form[13]
- CEP Attestations[13]
- List of Applicants[13]
- Master File (MF) Application Form for Human and Veterinary Drug and Clinical Trial Applications (CTAs)
- Agent Appointment Letter[13]
- Annotated Certified Product Information Document (CPID)[13]
- Non-annotated Certified Product Information Document (CPID)[13]
- Annotated Product Monograph (PM)
- Non-annotated Product Monograph (PM)
- Second language Product Monograph (PM)
- Post-Authorization Commitments table-
- Yearly Biologic Product Report (YBPR) schedule
- Company Core Data Sheet
- International registration, review and/or marketing status document
- Letter of Access (when correction is made as requested by HC or if the LoA is updated as per the Guidance Document: Master Files (MFs) –Procedures and Administrative Requirements. Sample LoA can be found in Appendix 2 of aforementioned guidance document)
- The Draft (mock-up) inner and outer labels (see Figure 8)
- The Final inner and outer label (see Figure 8) when provided with the Market Notification Form

The operation attribute for **all** content files provided to correct an error or missing information in a document should be **"replace".**

The operation attribute for completed forms (such as the HC-SC3011 form[14], fee form, submission certification form), should be:

- "**New**" when provided as part of the first transaction of a regulatory activity (such as NDS, ANDS).

[13] Should be provided only when changes applicable

[14] Single HC-SC3011 form containing all information for all applicable strengths.

- "**Replace**" when provided as additional information for a correction of an error in the form in response to Health Canada requests (i.e. OSIP queries, screening clarification, and SDN) or for a change in brand name or contact information.

The Pre-Submission Meeting should be:

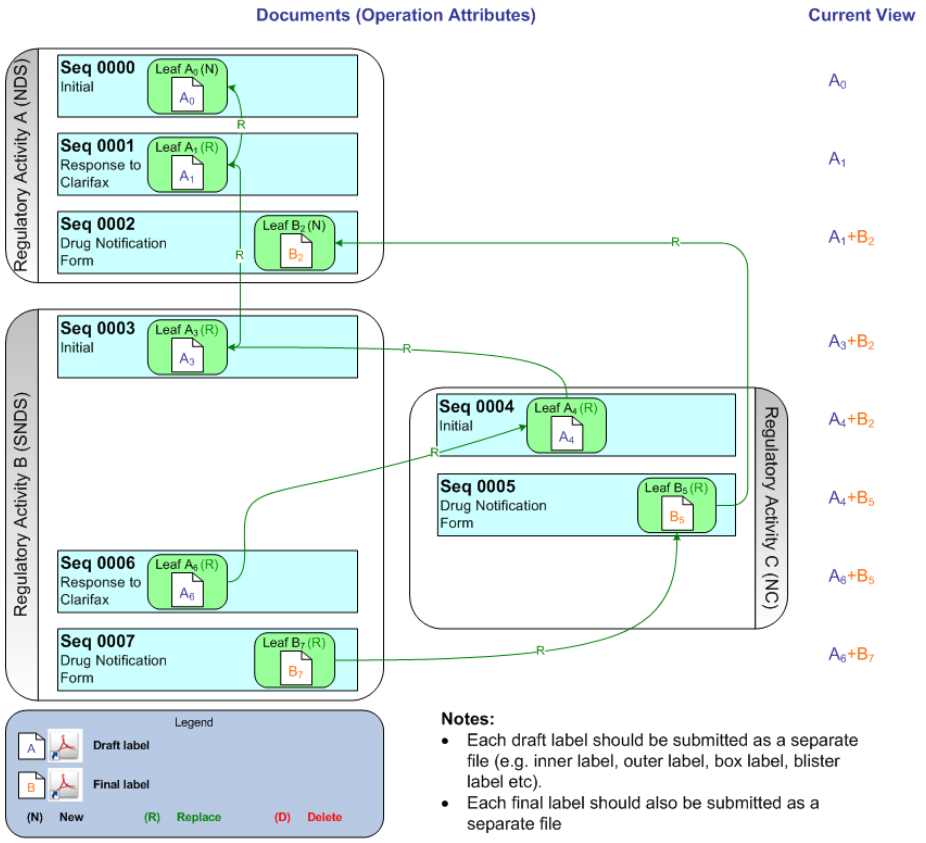
- "**New**" for all content files provided as part of the Pre-Submission Meeting Package, with the exception of the LCM table. When a document is revised in relation to a pre-submission meeting, the operation attribute should be "**replace**".
- "**New**" for all content files provided in an NDS/ANDS filed subsequent to a pre-submission meeting, with the exception of the LCM table. The NDS/ANDS should be a stand-alone regulatory activity. Any information provided in relation to pre-submission meeting, if needed in the NDS/ANDS, should be resubmitted, with the exception of meeting minutes, which may be hyperlinked.
- "**Replace**" for an SNDS/SANDS submitted subsequent to a pre-submission meeting, as needed in relation to the previous regulatory transactions (with the exception of any regulatory transactions related to pre-submission meetings). If the SNDS/SANDS is the first regulatory activity in eCTD format, other than the pre-submission meeting, the operation attribute in the leaf element should be "**new**" for all content files provided, with the exception of the LCM table. The SNDS/SANDS should be a stand-alone regulatory activity. Any information provided in relation to pre-submission meeting, if needed in the SNDS/SANDS, should be resubmitted, with the exception of meeting minutes, which may be hyperlinked.

Specifications for Public Release of Clinical Information (PRCI)

The operation attribute for documents provided as part of the PRCI transaction such as Proposed Reduction Control Sheet, Anonymization Report, documents in module 2 and module 5, should be:

- "**New**" when providing these files as part of the "final" redacted package.

Figure 9: Life Cycle Management Label Scenario



The operation attribute for the following documents must be **"delete"** when they are withdrawn:

- Letter of Access (LOA) for master file (LOA withdrawals)
- Health Technology Assessment (HTA)

3.4 Bookmarks in Portable Document Format (PDF) Files

It is important that PDF files be properly bookmarked. Rules of thumb for good bookmarking include:

- Documents of ten pages or more should be bookmarked.
- Bookmarks are equivalent to, and should be organized like a document table of contents, and should not include the regulatory activity level.
- Sections, subsections, tables, figures, and appendices should all be bookmarked.
- Too many levels of bookmarks are inefficient; in most instances, four levels of bookmarks should be sufficient:

1 Heading

1.1 Subheading

1.1.1 Sub-subheading

1.1.1.1 Sub-Sub-Subheading

Health Canada recognizes that bookmarks are generated automatically from document headings, but nevertheless recommends they be kept concise.

Public Release of Clinical information (PRCI): Bookmarks in PRCI transactions are not required. However if provided, after redaction of PRCI documents, bookmarks should be checked to ensure they are not broken.

3.5 Hyperlinks and Cross-References

In a regulatory activity in eCTD format, hyperlinks should be used wherever cross-references were used in the CTD format (e.g., annotations of PMs). The ICH Electronic Common Technical Document Specification requires other hyperlinks, which should also be added.

Hyperlinks should be provided throughout a regulatory activity to aid efficient navigation to annotations, related sections, publications, appendices, tables, and figures that are not located on the same page. Overuse of hyperlinks lengthens the processing of the regulatory transaction and may create confusion for the reviewers. Therefore, their use should be well thought out.

There should also be consistency in the way navigational aids are provided. Within each document, bookmarks and hyperlinks from the table of contents should be provided to all tables, figures, publications, and appendices.

With the exception of tables of contents, hyperlinks should be indicated typographically with blue text or a blue box around the text. Health Canada prefers that hyperlinks be spelled out as cross-references with explicit citations of module and section, as appropriate.

Hyperlinks are not expected for word-processed documents.

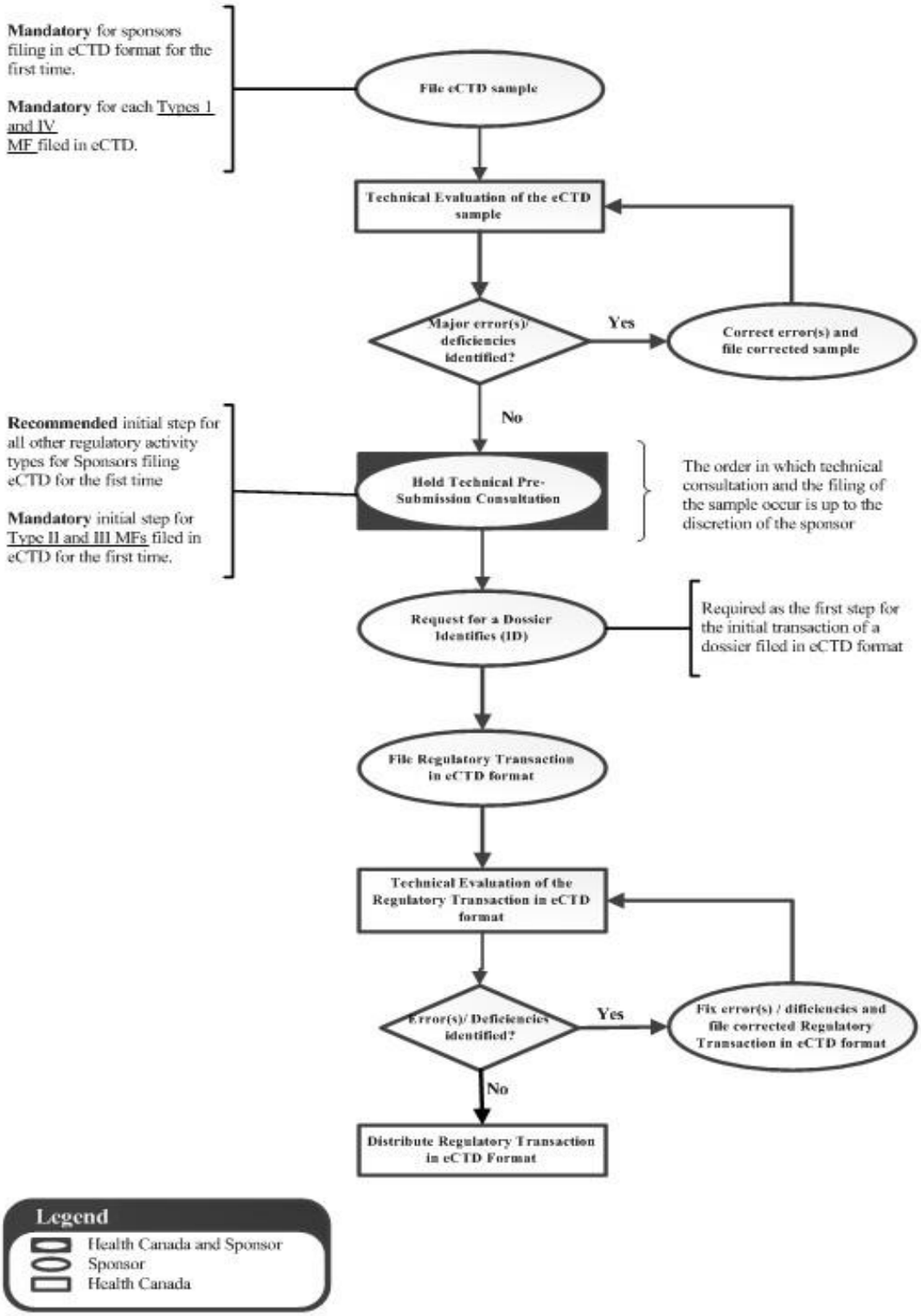
External hyperlinks currently result in a validation error that would normally cause a regulatory transaction to fail validation. However, including some links to a web page "www.*****" (such as sponsors own websites) or e-mail addresses "*****@****.**" are acceptable in some labelling documents and literature references. Any external links to information pertinent to the review process will result in a validation failure. Information pertinent to the review process should be included within the regulatory activity as a PDF or another appropriate file type.

Public Release of Clinical information (PRCI): Hyperlinks in PRCI transactions are not required. However, if provided, after redaction of PRCI documents, hyperlinks and cross-references should be checked to ensure they are not broken.

4. FILING PROCESS FOR REGULATORY TRANSACTIONS

The process for preparing and filing regulatory transactions in eCTD format is illustrated in figure 10. The steps discussed in the following subsections correspond to the process diagram.

Figure 10: Filing Process for Regulatory Transactions Document (eCTD) Format.



4.1 Filing an eCTD Sample

Sponsors filing a regulatory transaction (Such as: ANDS, NDS, DINA) using the eCTD format for the first time with Health Canada **must** file an eCTD sample transaction at least two months in advance of filing their formal regulatory transaction in eCTD format. This period is not part of, and will not delay, the review process. Analysis of the sample serve to identify and resolve potential technical issues before the actual transaction is filed. The filing of a sample in eCTD format for subsequent regulatory transactions will depend on various factors, including changes in ICH specifications, changes in the Health Canada Module 1 specifications, and changes in technology (e.g., file formats, new tools used by the sponsor to build the eCTD transaction).

Sponsors filing master file regulatory transactions in the eCTD format for the first time **must** file a sample for each Master file type (Types I to IV) prior to the formal regulatory transaction, regardless of the sponsor's experience with filing in eCTD format. The sample must mimic the actual regulatory transaction and should be created based on the information outlined in Appendix E.

Sponsors should not request a Dossier ID for a sample transaction. The Dossier ID for sample transaction must be an "s" followed by the date the sample was created, in the format yymmdd (e.g., s190621).

The sample transaction must be provided via the CESG. The sample transaction in eCTD format may be a partial regulatory activity, however, it must contain, at a minimum, the following files:

System generated files

- eCTD backbone file (index.xml)
- eCTD backbone MD5 checksum file (index-md5.txt)
- Canadian Module 1 Backbone file (ca-regional.xml)
- Canadian Module 1 Schema Version 2.2 (ca-regional-2-2.xsd, xml.xsd, xlink.xsd)
- ICH eCTD DTD (ich-ectd-3-2.dtd)

Content files

- Cover letter must be provided indicating the reason for filing, the name and valid email address of the individual to whom follow-up emails should be addressed. In the absence of the email address, the sample will not be processed.
- Other files and documents for all relevant modules are recommended.
- If a sponsor intends to include Study Tagging Files in the formal regulatory transaction, they should also be included in the sample transaction. Otherwise, the sample transaction should include node extensions.
- For master files, follow the illustrations provided in Appendix E, and provide content files in sections based on the actual transaction.

4.2 Technical Pre-Submission Consultation

Sponsors filing a regulatory activity in eCTD format for the first time are recommended to request a technical pre-submission consultation with Health Canada. However, a technical pre-submission consultation is **mandatory** for MFs Type 2 and 3 when each type is filed in eCTD for the first time.

This consultation is held to clarify needs, responsibilities and expectations, as well as to enable Health Canada the opportunity to provide feedback on the sample transaction in eCTD format. This consultation does not necessarily need to take place at the same time as the regulatory pre-submission meeting, and may be conducted if a sample transaction in eCTD format is not required.

To request a technical pre-submission consultation, contact Health Canada at hc.ereview.sc@canada.ca.

Sponsors should include the following information in their requests:

- The purpose of the meeting;
- A brief description of the product to be discussed at the meeting;
- Three proposed dates for the meeting, including whether an afternoon or morning meeting is being requested;
- An agenda for the meeting;
- The names of sponsor representatives attending the meeting.

Upon receipt of the above information, Health Canada will schedule a teleconference or WebEx.

4.3 Technical Evaluation of the eCTD Sample

Upon receipt, Health Canada conducts the technical evaluation for the sample in eCTD format to ensure that it conforms to the requirements outlined in this guidance document, Health Canada's Guidance Document: Creation of the Canadian Module 1 Backbone, and the ICH Electronic Common Technical Document Specification.

The technical evaluation process for samples is the same process as actual regulatory transactions described in section 4.7.

During this evaluation process, the content of the sample regulatory transaction is not reviewed.

Written feedback will be issued to the sponsor for each technical evaluation of the sample transaction.

4.4 Correct Errors and File Corrected Sample

If Health Canada has identified major errors and/or deficiencies during the technical evaluation, the sponsor files the corrected eCTD sample as the same sequence 0000. If the sponsor wishes to discuss the evaluation, they should contact Health Canada at hc.ereview.sc@canada.ca.

Health Canada will evaluate the corrected sample and send a written technical evaluation to notify the sponsor of any required technical changes prior to the sponsor filing the regulatory activity in eCTD format. This process is iterative. Health Canada will work with the sponsor to increase the probability of an error-free regulatory activity in eCTD format.

4.5 Request for Dossier Identifier

Prior to filing the first regulatory transaction for a dossier in eCTD format, the sponsor must submit a Dossier ID Request Form using the online form (see Section 2.3.1, "Top Level Folder and Dossier Identifier").

For Master Files, a Dossier Identifier must be requested by sending an email to hc.ereview.sc@canada.ca. The email request must include a fully completed MF application form as an attachment.

Note that the requirement to obtain a Dossier Identifier from Health Canada does not apply to sample transactions (see Section 4.1, "File eCTD Sample").

4.5.1 Re-Issuance of dossier IDs:

Dossier IDs that have not been used within **18 month** of their issuance are **automatically** deleted from Health Canada's tracking system, without any notification to the sponsor. If a sponsor intends to use a dossier ID that has been deleted a new dossier ID request form will be required; however, the request should indicate the previously issued dossier ID.

To verify the status of the dossier ID, log in to Health Canada's Drug Submission Tracking System – Industry Access (DSTS-IA). For information regarding DSTS-IA, or for an account set-up, please

contact the Office of Submission and Intellectual Property by sending an e-mail to: hc.client.information.sc@canada.ca.

4.6 Signatures provided with Regulatory Transactions

The documents that legally require a signature should be printed, signed, scanned, and saved as PDF files, then included in the regulatory transaction.

If only one page of a multi-page document contains a signature, the sponsor should scan that page and then include the scanned page at the same location in the PDF file of the document. Each document should have only one PDF file.

Certain Health Canada documents may have alternate instructions for signatures such as the electronic PDF fillable forms available on the Health Canada website, e.g. Certificate of Suitability (CEP), CEP attestation, or a letter of access (LOA).

Health Canada no longer requires signature on the cover letter. However, continue providing contact information, including printed name, phone/fax number, and email address.

4.7 Technical Evaluation of a Regulatory Transaction

Upon receipt of a regulatory transaction, Health Canada performs a technical evaluation to ensure that it conforms to the requirements outlined in this and other relevant documents available on the Filing submissions electronically information page.

The technical evaluation process has three stages:

4.7.1 CESG compliance

The first stage of the technical evaluation consists of verifying the folder structure (use of top level folder) and technical aspects of the transaction as per the CESG requirements. (refer to CESG information page for details).

Written communication (in some cases with attached eCTD Validation Report) will be sent to the sponsor if there are issues encountered at this stage; for example if there is a missing top level folder, if the file path is too long, or if Health Canada is not able to extract the content of the transaction.

4.7.2 Technical validation

The second stage of the technical evaluation is conducted by a validation software. The technical validation of the regulatory transaction according is performed using the latest published validation rules for the eCTD format.

If technical validation fails, an eCTD Validation Report describing the errors will be issued to the sponsor for that regulatory transaction. The validation report will be sent in a .zip format.

If the validation reported only identifies warnings, a report will not be sent to the sponsor.

4.7.3 Manual verification

The third stage is a manual verification of the particular regulatory transaction type, and includes, but is not limited to, verifying the following:

- Placement of documents, particularly in module 1 (refer to Organization and Document Placement for Canadian Module 1)
- Use of:
  - operation attributes,

- element attributes,
- leaf titles,
- node extensions (for modules 1, 3 and 5), and
- Study Tagging Files (for modules 4 and 5).

as per information in this guidance and the ICH 3.2.2 eCTD Specifications document.

During this verification process, the document content of the regulatory transaction is not reviewed.

Written communication will be sent to the sponsor if there are issues encountered at this stage. Feedback will be provided according to the timelines for processing, as per the Guidance Document: Management of Drug Submissions and Applications.

Upon receipt of written communications from Health Canada, sponsors may reply to the email if they wish to further discuss the errors and/or deficiencies.

Reminder: Ensure to indicate a valid email address on the cover letter where any correspondence regarding your transaction must be sent. It is up to the sponsor to ensure that the revised/new sequence as per the request is submitted to Health Canada in timely manner.

4.8 Filing Corrected Regulatory Transactions

When required, the sponsor must correct the previously submitted regulatory transaction and re-file it to Health Canada. Upon receipt by Health Canada, the re-filed transaction undergoes technical evaluation again. This process is iterative.

If a transaction fails technical evaluation, the sequence number does not change when the corrected transaction is re-filed.

If the regulatory transaction passes technical evaluation but has other content deficiencies (identified during processing, screening or review), then responses to any Health Canada issued correspondence (e.g. clarification request, SDN, or on process hold) require an increment to the sequence number.

4.9 Distribution of Regulatory Transactions at Health Canada

When the technical evaluation of the regulatory transaction has been completed, the administrative, screening, and/or evaluation process is initiated.

5. IMPORTANT CONSIDERATIONS WHEN PREPARING REGULATORY ACTIVITIES IN eCTD FORMAT

This section has been developed to provide additional details on specific items, which have either received frequent questions, or encountered numerous issues during technical evaluation.

1. Issues found during the technical evaluation (section 4.7) such as CESG compliance issues, technical validation errors, or manual verification issues will result in Health Canada sending a validation report and/or verification email. To correct such errors and issues, the sponsors are required to correct the failed sequence and re-file the **same number sequence**.

   However, if Health Canada is requesting missing documents, new documents, or correction to the documents, (identified during processing, screening or review) then responses to any Health

Canada issued correspondence (e.g. clarification request, SDN, or on process hold) require an **increment to the sequence number**.

2. The content of the regulatory activity in eCTD format is the legal document; therefore emails provided directly to reviewers have no legal value and will not be uploaded on the Health Canada internal systems as they are only considered a convenience copy.

   With the exception of the second language PM, all information submitted as part of a dossier must be provided in eCTD format via the CESG the same day as a convenience copy is sent via email. This process will complete the legal document for the dossier and ensure there are no delays with the issuance of the NOC.

3. When a regulatory transaction has been filed and accepted by Health Canada, it should not be revised without prior consultation.

4. Filing of additional information/regulatory transactions:

   - Once a sponsor files a regulatory activity in eCTD format, all additional information and subsequent regulatory activities for the **same dossier must** also be filed in eCTD format. Sponsors should not revert to non-eCTD electronic only format.
   - Separate responses to solicited information should be provided individually for each request and should not be bundled in one transaction.
   - Only one response document (Q&A) should be created to respond to all questions in a particular request
   - Regulatory activities provided to MHPD (e.g. PSUR, PBRER, RMP-PV) must be filed as separate regulatory transactions, even if a single request for multiple Post-market Vigilance data has been issued by MHPD.

5. A sponsor may have filed regulatory activities in "non-eCTD electronic-only" format, have the information approved, and intends to file subsequent regulatory activities (e.g., SNDS, SANDS, NC, Level III) in the eCTD format. In such cases, the sponsor is not expected to refile the previously approved regulatory activities in eCTD format.

6. 'Pre-Submission Meeting Request' should be the first transaction filed in eCTD format for pre-submission meetings (see Section 3.3).

7. Element Attributes for Modules 2, 3 and 5:

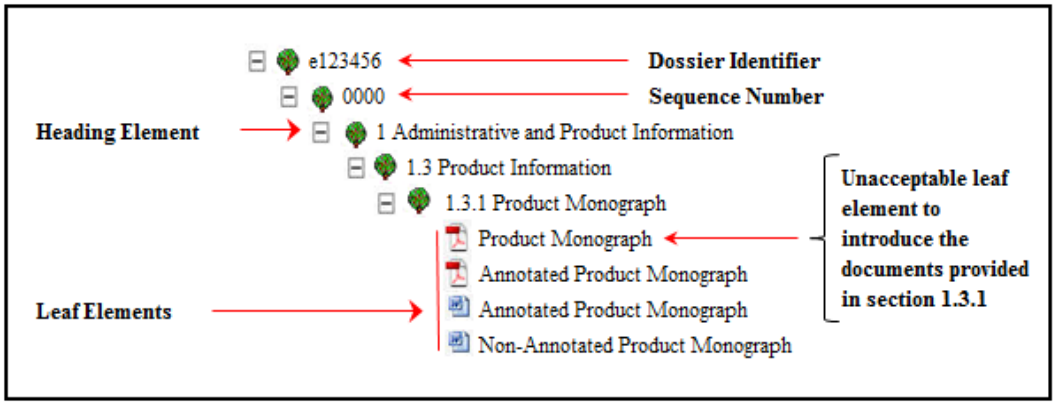
   - There is currently no standard terminology for element attributes; however, sponsors should choose these attributes carefully as they cannot be easily changed during the life cycle of the dossier.
   - A slight modification to an element attribute will create a duplicate heading element (node), therefore:
     - Attributes should be left as they have been written in the first regulatory transaction where they were defined. Keep in mind that attributes are case-sensitive (e.g., [Nausea] [nausea]).
     - Attributes should not be changed when the company has undergone a company name change.
     - Typographical mistakes should not be corrected.

For further information regarding element attributes, refer to Table 6-9, 6-10 and 6-11 of section "eCTD Element/Attribute Instructions" in Appendix 6 of the ICH Electronic Common Technical Document Specification (Version 3.2.2).

8. Leaf Elements:

   - A leaf element must **not** be used to indicate that a section (heading or subheading element) is not applicable. The heading elements that have no content should not be included.
   - A leaf element must **not** be used at the beginning of a section (heading or subheading element) to introduce the document(s) provided in the section.

Figure 11: Unacceptable Leaf Elements



9. MF Holders or authorized MF Agents may convert their MF dossiers from the non-eCTD electronic format to the eCTD format. As a **baseline** requirement for the convertion, the MF Holder or authorized MF Agent must include the entire MF in the first eCTD transaction (sequence 0000). It is not sufficient to convert the MF by simply submitting the next transaction in eCTD format (i.e., submitting an LOA or update in eCTD format as a subsequent transaction for an MF currently in non-eCTD format).

10. When providing MF Types I, II, III & IV, the folders in Module 1 will be considered as the Restricted Part (RP). See Appendix E for illustrations.

11. When submitting multiple patent forms (Form IVs and the Form Vs) related to the Patented Medicines (Notice of Compliance) regulations as new or to replace previously submitted forms:

    - The multiple forms should be submitted in one sequence;
    - The forms should always be submitted using the original regulatory activity type (NDS, ANDS).

    When submitting written correspondence related to the Patented Medicines (Notice of Compliance) Regulations or consent letters, the document:

    - Should be submitted in one sequence;
    - Should always be submitted using the original regulatory activity type (NDS, ANDS).

    Submitting patent forms or written correspondence for older activities that were submitted in paper and converted to eCTD must be submitted in eCTD format.

12. The First Language Pristine Product Monograph is no longer accepted by Health Canada. As per the current process, the Health Canada Approved First Language PM and the **sponsor provided**

second language version will continue to be uploaded on the Drug Product Database (DPD), for public access.

13. Regulatory Transactions (eCTD sequences) must be sent to Health Canada in consecutive order via the CESG.
    a. When sending two transactions/sequences for the same dossier on the same day (i.e. e123456 – 0001 and 0002), the sponsor must ensure they have received all the acknowledgment receipts for the first transaction (sequence 0001) prior to sending the next transaction (sequence 0002).
    b. If Health Canada receives two eCTD transactions for the same dossier, and the first one has failed technical evaluation (see section 4.7), both eCTD transactions (sequence 0001 and 0002) will have to be resent.
14. If a sponsor is filing transactions using the regulatory enrolment process (REP), requirements for certain documents (e.g. HC-SC3011 form, fee form, cover letter) may differ from that which is prescribed in this document. For such cases, instructions in the REP guidance document will supersede this document. Refer to the REP information page for more details.
15. Health Canada has selected a commercial off-the-shelf solution for its internal eCTD viewing tool. Sponsors will not be provided access to the Health Canada eCTD viewing tool.
16. Health Canada will not provide style sheets to sponsors to enable the viewing of eCTD XML files.

Appendix A: Reference Documents

Health Canada References

The latest versions of the documents below as well as other guidance documents, policies, notices, templates, and forms can be obtained from the Health Canada website.

Guidance documents on electronic regulatory activities can be found on Filing Submissions Electronically information page.

General

- Validation rules for regulatory transactions submitted to Health Canada in the electronic Common Technical Document (eCTD) format
- Guidance Document: Creation of the Canadian Module 1 Backbone
- Canadian Module 1 Schema Version 2.2
- Guidance Document: Management of Drug Submissions
- Frequently Asked Questions - Common Electronic Submissions Gateway
- How to Pay Fees to Health Products and Food Branch (HPFB)
- Guidance Document: Post-Notice of Compliance (NOC) Changes: Framework Document
- Guidance Document: Post-Notice of Compliance (NOC) Changes: Quality Document
- Guidance Document: Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document
- Notice –Revision to the Post-Notice of Compliance (NOC) Changes: Notices of Change Level III Form
- Guidance Document - New requirements for submitting administrative drug submissions to Health Canada
- Guideline on Preparation of Drug Identification Number Submissions
- Guidance Document on Post-Drug Identification Number (DIN) Changes
- Preparation of Proposed Redaction and/or Final Redaction Package Submission in eCTD/CTD format for the Public Release of Clinical Information
- Changes in Manufacturer's Name and/or Product Name
- Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format
- Guidance for Industry: Preparation of the Quality Information for Drug Submissions in the CTD Format: Conventional Biotherapeutic Products
- Guidance Document - Regulatory Requirements for Drug Identification Numbers (DINs)
- Guidance Document: Master Files (MFs) – Procedures and Administrative Requirements
- Guidance Document: Reconsideration of Decisions Issued for Human Drug Submissions
- Drug Good Manufacturing Practices (GMP), and the Establishment Licensing (EL) Enforcement Directive (POL-0004).
- Good Manufacturing Practices (GMP) Guidelines (GUI-0001) -2009 Edition, Version 2
- Notice: Submission Filing Requirements - Good Manufacturing Practices (GMP) / Drug Establishment Licences (DEL)
- Guidance document Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice
- Guidance Document Product Monograph
- Guidance for Industry - Review of Drug Brand Names
- Guidance for Industry - Priority Review of Drug Submissions
- Guidance Document Notice of Compliance with Conditions (NOC/c)
- Guidance Document: Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)

- Notice Regarding Implementation of Risk Management Planning including the adoption of International Council on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E
- Guidance for Sponsors - Lot Release Program for Schedule D (Biologic) Drugs
- Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs
- Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications

International Council on Harmonization (ICH) References

The ICH guidelines have been adopted by Health Canada and can be obtained from the ICH website at www.ich.org.

For information on electronic standards, refer to the Electronic Standards (ESTRI) web site at: https://www.ich.org/page/electronic-standards-estri.

The eCTD v3.2.2 related information are posted on the ICH M8's web site at: http://ich.org./page/multidisciplinary-guidelines.

- Electronic Common Technical Document Specification (Version 3.2.2)
- Study Tagging File Specification and Related Files
- Specification for Submission Formats for eCTD

The Common Technical Document (CTD) related information can be obtained in the M4 section of the ICH website: https://www.ich.org/page/ctd . The Information are broken down to four main categories:

- M4: Organization
- M4Q: Quality
- M4S: Safety
- M4E: Efficacy

Appendix B: Definitions

Additional Information: both solicited and unsolicited information.

- Solicited information such as: responses to SDN, NOD, NON, or Clarification Request (telephone request, email request, screening Acceptance Letter).
- Unsolicited information such as safety information and changes in the name of the sponsor or product during review.

Note: For more details about solicited and unsolicited information, see Section 12.0 and 14.0 of Health Canada's Guidance Document: Management of Drug Submissions and Applications respectively.

Administrative change submission: a regulatory activity pertaining to a change in manufacturer's name and/or product name following a merger, buy-out or other corporate restructuring or as a result of a licensing agreement, that does not require scientific review.

Confidential Business Information: Information which provides a business advantage as a result of the fact that it is kept confidential. This is true whether the information is tangible or intangible. Confidential business information is broad enough to encompass trade-secrets.

Dossier: A collection of all regulatory activities throughout the life cycle of a product for a stakeholder. For clinical trials it is a collection of all regulatory activities throughout the life cycle of a single clinical trial protocol.

Dossier Identifier: Lowercase letter followed by six (6) or seven (7) unique numbers depending on the regulatory activity type.

Labelling submission: a regulatory activity that requires a scientific review to support a name change for the drug product.

Leading Sheet: A document describing the information being provided (e.g. a document stating "this sub-folder contains the following documents…").

Market Notification Form (also known as Drug Notification Form): as per section C.01.014.3 of the Food and Drug Regulations, companies are required to notify Health Canada of a drug being sold.

Master File (MF): is a reference that provides information about specific processes or components used in the manufacturing, processing, and packaging of a drug.

Novel Excipient: is an excipient which is being used for the first time in a drug product, or by a new route of administration (from ICH). It may be a new chemical entity or a well-established one which has not yet been used for human administration and / or a particular human administration pathway in Canada and/or outside Canada.

Regulatory Activity: a collection of all regulatory transactions throughout the process of a specific activity which includes, but is not limited to, NDS, ANDS, DIN Application, YBPR.

Regulatory Transaction: Any information package sent by the stakeholder as part of a regulatory activity such as initial data, unsolicited and solicited data (e.g. response to a clarification request, NON, NOD, pristine PM, DNF).

Stakeholder: Company, **Sponsors/DIN owner/Manufacturer of pharmaceutical or biological drug** for regulatory activities filed according the Food and Drug Act and Regulation, **Owner/Agent/Manufacturer for Master File**, and **Manufacturer of Medical Devices** for regulatory activities filed according to the Medical Devices Regulations and the Food and Drugs Act.

Applicant's Part - The non-confidential business information contained in an MF, formerly called the Open Part (see Section 2.4.2.2).

Restricted Part - The confidential business information (CBI) contained in an MF, formerly called the Closed Part (see Section 2.4.2.2).

Appendix C: Example of a Life Cycle Management Table

Example of Pharmaceutical or Biologic dossiers

Company Name:	Pharmacompany				
Brand Name:	Drug X				
Dossier Identifier:	e123454				
Sequence Number (most recent last)	**Date Submitted** (mmm. dd, yyyy)	**Control Number**	**Related Sequence**	**Regulatory Activity Type**	**Sequence Description**
0000	Dec. 17, 2003	123454	----	MPNDS	Pre-Submission Meeting Request
0001	Jan. 15, 2004	123454	0000	MPNDS	Pre-Submission Meeting Package
0002	Feb. 29, 2004	123454	0000	MPNDS	Minutes of Meeting, Feb. 15, 2004
0003	May 10, 2004	123455	----	PRNDS	Priority Review Request
0004	Jul. 05, 2004	123456	----	NDS	INITIAL
0005	Jul. 10, 2004	123456	0004	NDS	Response to Processing Clarification Request dated Jul. 07, 2004
0006	Nov. 03, 2004	123456	0004	NDS	Response to NOD dated Sep. 25, 2004
0007	Feb. 22, 2005	123456	0004	NDS	Response to Clinical Clarification Request dated Feb. 11, 2005
0008	Apr. 11 , 2005	123456	0004	NDS	Unsolicited Data, Change in the Name of Sponsor
0009	Apr. 20, 2005	123456	0004	NDS	Response to Quality Clarification Request dated Apr. 6, 2005
0010	May. 25, 2005	123456	0004	NDS	Response to Labelling Clarification Request dated May 15, 2005
0011	Jan. 09, 2006	123555	----	SNDS	Post NOC Change
0012	Jul. 5, 2006	123555	0011	SNDS	Response to NON dated Jun. 8, 2006
0013	Jul 27, 2006	123666	----	SNDS	Post NOC Change
0014	Sep. 10, 2006	123555	0011	SNDS	Response to Quality Clarification Request dated Sep. 01, 2006
0015	Oct. 15, 2006	123679	----	PSUR-PV	For Period of Sep. 15, 2005 to Sep. 14, 2006
0016	Oct. 17, 2006	123666	0013	SNDS	Response to Labelling Clarification Request dated Oct. 12, 2006

0017	Oct. 20, 2006	123666	0013	SNDS	Response to Telephone Request dated Oct. 15, 2006
0018	Oct. 26, 2006	123666	0013	SNDS	Response to Labelling Clarification Request dated Oct. 20, 2006
0019	Dec. 12, 2006	----	----	Level III	2006, 15, 19a.
0020	Mar. 5, 2007	123721	----	YBPR	For Period of Jan. 25, 2006 to Jan. 24, 2007

Example of life cycle management table for master file dossiers

Company Name:	Master file holder name	
Master File Name:	Master file Name	
Dossier ID:	e123456	
Sequence Number (most recent last)	**Date Filed** (mmm. dd, yyyy)	**Sequence Description**
0000	Jan. 10, 2017	New **or** Conversion **or** Conversion and Update
0001	Jan. 30, 2017	Response to Processing Clarification Request dated Jan. 25, 2017
0002	Mar. 15, 2017	Letter of Access
0003	June 21, 2018	Update
0004	September 6, 2018	Withdrawal of Letter of Access
0005	December 15, 2018	Administrative Change
0006	April 1, 2019	Update
0007	May 30, 2019	Response to Quality Clarification Request dated May 20, 2019

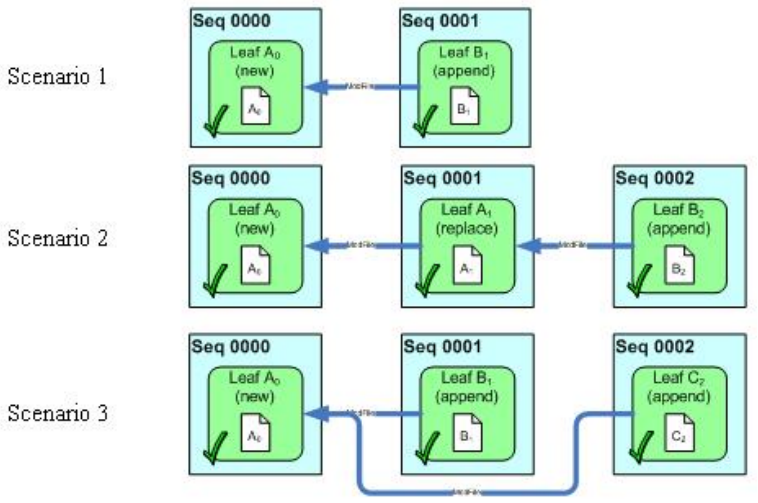
Appendix D: Life Cycle Management Scenarios for Operation Attributes

The scenarios provided in this appendix describe rules applicable to the general use of the operation attribute for life cycle management. They are examples from a broad range of possibilities. They are not intended to be a comprehensive set and merely address some common situations that sponsors are likely to encounter.

Table D-1: Valid Append Scenarios

Scenario Number and Description			Attributes			
	Seq. #	Leaf ID	File Ref.	Operation	Mod. File	Comment
1. Append to a New leaf (EDMS 10)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	B1	B1.pdf	append	A0	Valid append
2. Append to a Replace leaf (EDMS 21)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	A1.pdf	replace	A0	Valid replace
	0002	B2	B2.pdf	append	A1	Valid append to replace
3. Parallel Appends to a New leaf (EDMS 28)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	B1	B1.pdf	append	A0	Valid append
	0002	C2	C2.pdf	append	A0	Valid append

Figure D-1: Valid Append Scenarios



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

Table D-2: Invalid Append Scenario

Scenario Number and Description	Seq. #	Leaf ID	Attributes			Comment
			File Ref.	Operation	Mod. File	
4. Append to an Append leaf (EDMS 29)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	B1	B1.pdf	append	A0	Valid append
	0002	C2	C2.pdf	append	B1	Invalid append

Figure D-2: Invalid Append Scenario

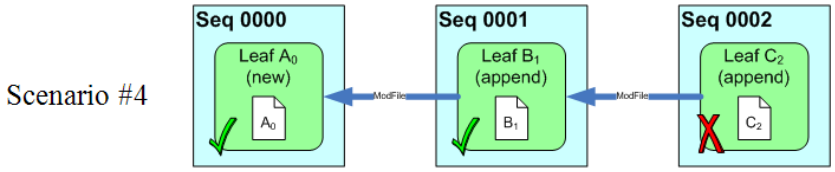


Table D-3: Valid Replace Scenarios

Scenario Number and Description	Seq. #	Leaf ID	Attributes			Comment
			File Ref.	Operation	Mod. File	
5. Replace a New leaf (EDMS 8)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	A1.pdf	replace	A0	Valid replace
6. Replace a Replace leaf (EDMS 19)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	A1.pdf	replace	A0	Valid replace
	0002	A2	A2.pdf	replace	A1	Valid chain replace
7. Replace an Append leaf (ETICS 3, EDMS 27)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	B1	B1.pdf	append	A0	Valid append
	0002	C2	C2.pdf	replace	B1	Valid replace
8. Replace a New leaf that has an Append leaf, with a leaf that consolidates the content of both (ETICS 2, EDMS 26)*	0000	A0	A0.pdf	new	Empty	Valid new
	0001	B1	B1.pdf	append	A0	Valid append
	0002	C2	C2.pdf	replace	A0	Valid replace
		B2	Empty	delete	B1	Mandatory delete

*When replacing the original document, any appended document must be deleted. Therefore the content of A0.pdf and B1.pdf should be consolidated.

Figure D-3: Valid Replace Scenarios

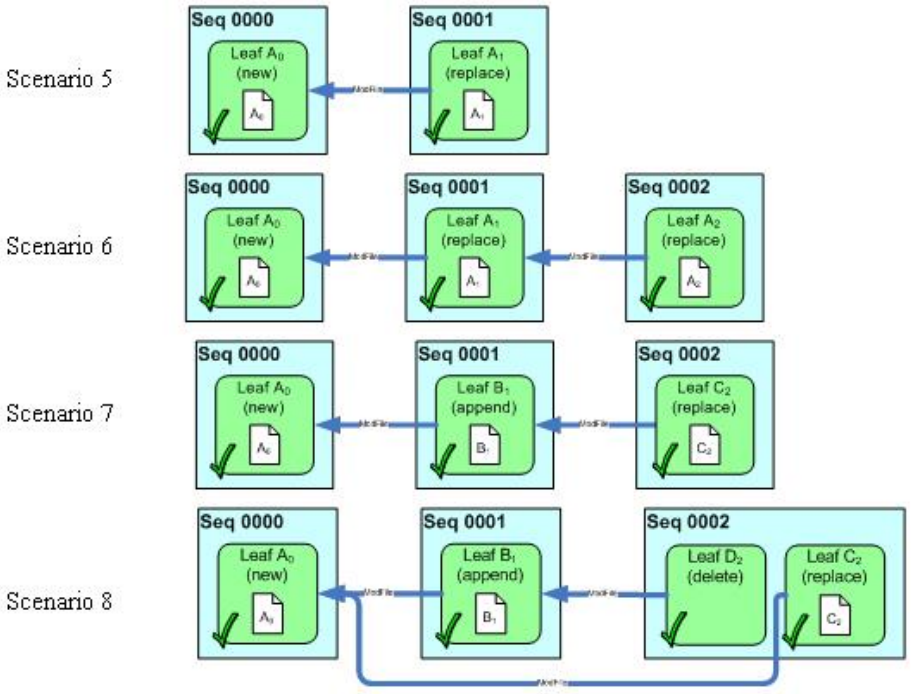


Table D-4: Valid Delete Scenarios

Scenario Number and Description			Attributes			
	Seq. #	Leaf ID	File Ref.	Operation	Mod. File	Comment
9. Delete a New leaf (EDMS 9)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	Empty	delete	A0	Valid delete
10. Delete a Replace leaf (EDMS 20)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	A1.pdf	replace	A0	Valid replace
	0002	A2	Empty	delete	A1	Valid delete replace
11. Delete an Append leaf (EDMS 30)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	B1	B1.pdf	append	A0	Valid append
	0002	A2	Empty	delete	B1	Valid delete
12 Delete a New leaf that has an Append leaf (ETICS 1, EDMS 25)*	0000	A0	A0.pdf	new	Empty	Valid new
	0001	B1	B1.pdf	append	A0	Valid append
	0002	C2	Empty	delete	A0	Valid delete
		D2	Empty	delete	B1	Mandatory delete

*When the original document is deleted, any appended documents must be deleted.

Figure D-4: Valid Delete Scenarios

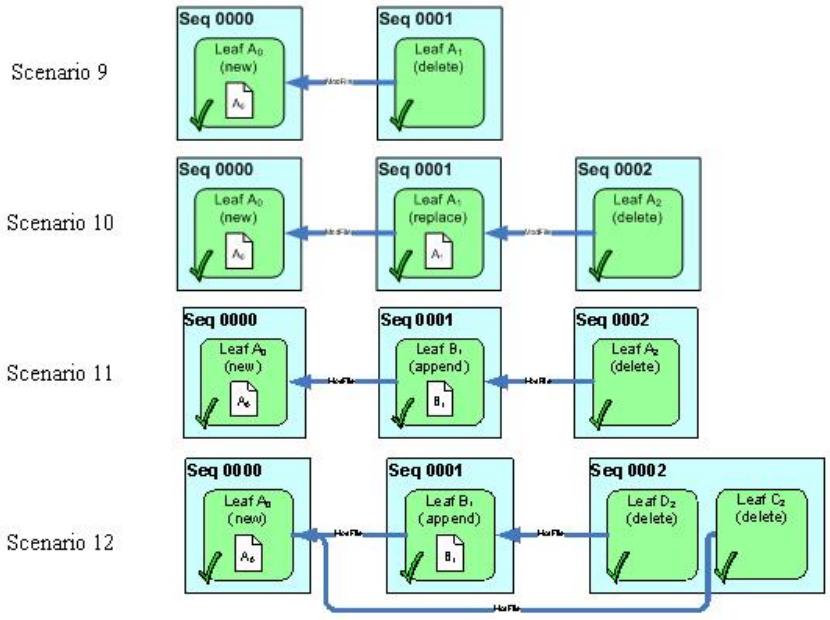


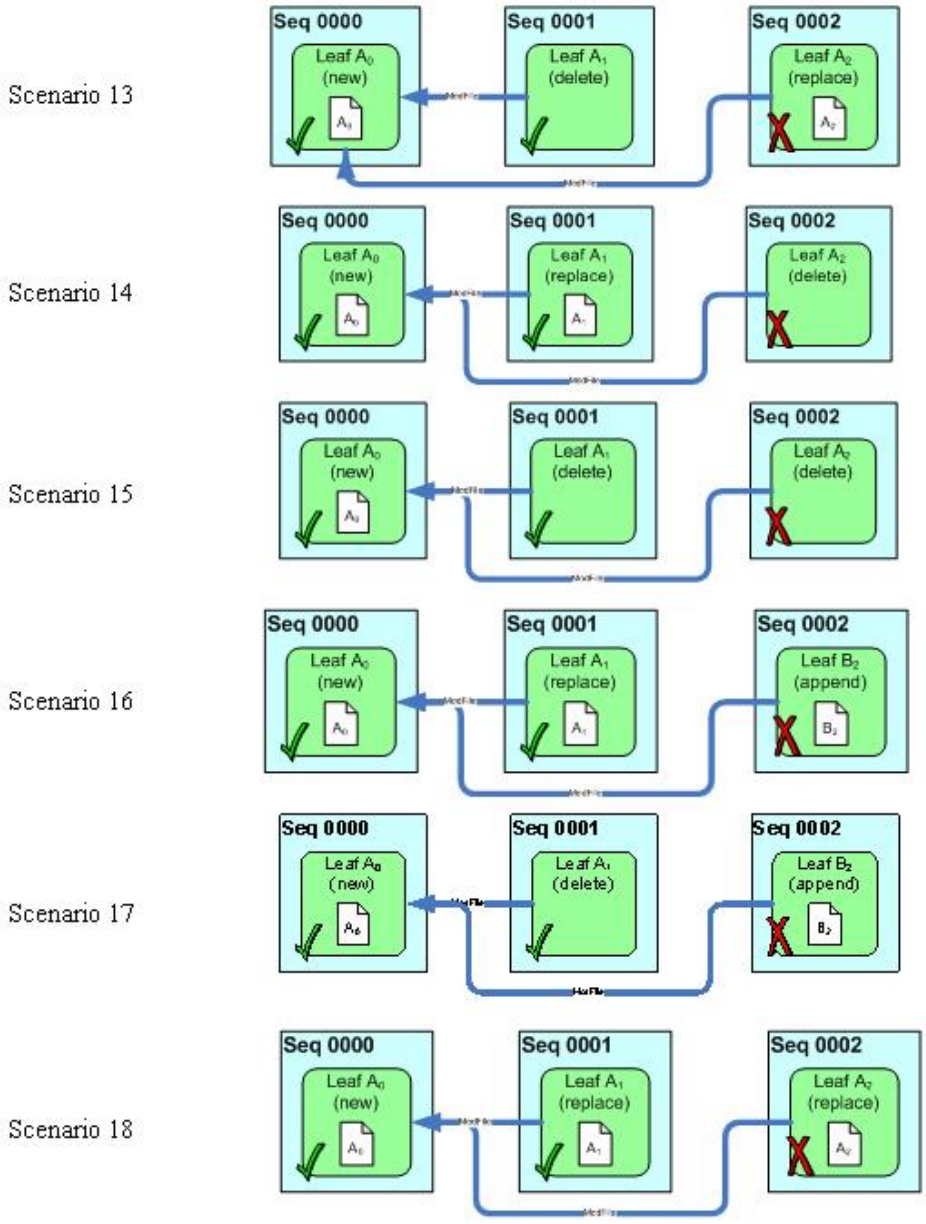
Table D-5: Invalid Operations on Non-current Leaves

As a general principle, an operation should not be applied to a leaf that is no longer active , and has been replaced or deleted.

Scenario Number and Description			Attributes			
	Seq. #	Leaf ID	File Ref.	Operation	Mod. File	Comment
13. Attempt to Replace a New leaf that has been Deleted (EDMS 31)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	Empty	delete	A0	Valid delete
	0002	A2	A2.pdf	replace	A0	Cannot undelete leaf
14. Attempt to Delete a New leaf that has been Replaced (EDMS 32)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	A1.pdf	replace	A0	Valid replace
	0002	A2	Empty	delete	A0	Must act on current leaf
15. Attempt to Delete a New leaf that has already been Deleted (EDMS 33)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	Empty	delete	A0	Valid delete
	0002	A2	Empty	delete	A0	Cannot re-delete leaf
16. Attempt to Append to a New leaf that has already been Replaced (EDMS 34)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	A1.pdf	replace	A0	Valid replace
	0002	B2	B2.pdf	append	A0	Must act on current leaf
17. Attempt to Append to a New leaf that has already been Deleted (EDMS 35)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	Empty	delete	A0	Valid delete
	0002	B2	B2.pdf	append	A0	Cannot undelete leaf
18. Attempt to Replace a New leaf that has already been Replaced (EDMS 36)	0000	A0	A0.pdf	new	Empty	Valid new
	0001	A1	A1.pdf	replace	A0	Valid replace
	0002	A2	A2.pdf	replace	A0	Undefined replace

*When the original document is deleted, any appended documents must be deleted.

Figure D-5: Invalid Operations on Non-current Leaves



Appendix E: Master Files (MF)

This section includes sample eCTD structures of various MF regulatory transactions to provide further guidance in addition to the content in section "2.4.3 Master Files Dossiers".

Note: When converting an existing MF (all types) to eCTD without providing any updates, the fee form is not required.

TYPE I – DRUG SUBSTANCE MASTER FILES

1. All documents in this folder will be considered as Restricted Part (RP) of the MF.
2. Two separate documents should be included in the folder "2.3 Quality Overall Summary", a "QOS (RP)" and a "QOS (AP)" files. They must be provided in PDF and Word formats.

Figure E-1: Sample eCTD structure for a Type I MF

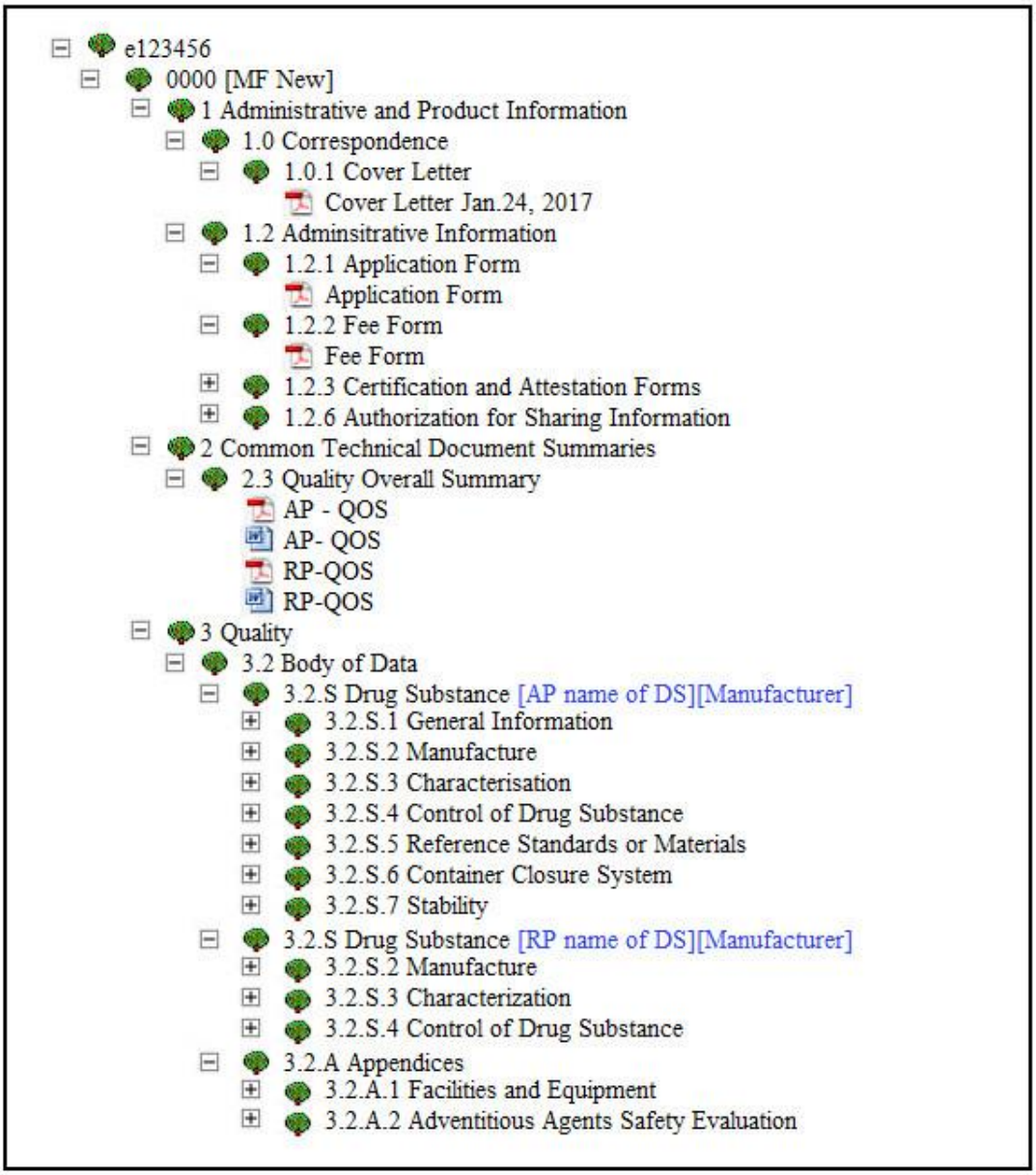


Table E-1: Distribution of MF Information between the Applicant and Restricted Parts for Type 1 - Drug Substance

Module/ Folder Names		Proposed 2015 Applicant's Part	Proposed 2015 Restricted Part
Module 1: Administrative and Product Information			
1.0	**Correspondence**		
1.0.1	Cover Letter	-	√
1.0.2	Life Cycle Management Table (Only required for eCTD)	-	√
1.0.3	Copy of Health Canada Issued Correspondence	-	√
1.0.4	Health Canada Solicited Information	-	√
1.0.7	General Note to Reviewer	-	√
1.1	Table of Contents (Only required for non-eCTD))	-	√
1.2	**Administrative Information**		
1.2.1	Application Forms	-	√
1.2.2	Fee Forms	-	√
1.2.3	Certification and Attestation Forms	-	√
1.2.5	**Compliance and Site Information**		
1.2.5.2	Establishment Licensing	-	√
1.2.5.5	Good Manufacturing Practices	-	√
1.2.6	Authorization for Sharing Information	-	√
1.2.7	International Information	-	√
1.3	**Product Information**		
1.3.6	Certified Product Information Document	-	√
Module 2: Common Technical Document Summary			
2.3	**Quality Overall Summary (QOS)**[1]	√	√
Module 3: Quality			
3.1	**Table of Contents of Module 3** (Not required for eCTD)	√	√
3.2	**Body of Data**		
3.2.S	**Drug Substance**		
3.2.S.1	**General Information**		
3.2.S.1.1	Nomenclature	√	-
3.2.S.1.2	Structure	√	-
3.2.S.1.3	General Properties	√	-
3.2.S.2	**Manufacture**		
3.2.S.2.1	Manufacturer(s)	√	-
3.2.S.2.2	Description of Manufacturing Process and Process Controls	√ [2]	√ [3]
3.2.S.2.3	Control of Materials	-	√
3.2.S.2.4	Controls of Critical Steps and Intermediates	√ [4]	√ [5]
3.2.S.2.5	Process Validation and /or Evaluation	-	√

Module/Folder Names		Proposed 2015 Applicant's Part	Proposed 2015 Restricted Part
3.2.S.2.6	Manufacturing Process Development	-	√
3.2.S.3	**Characterisation**		
3.2.S.3.1	Elucidation of Structure and other Characteristics	√	-
3.2.S.3.2	Impurities	√	√ [6]
3.2.S.4	**Control of Drug Substance**		
3.2.S.4.1	Specification	√	-
3.2.S.4.2	Analytical Procedures	√	-
3.2.S.4.3	Validation of Analytical Procedures	√	-
3.2.S.4.4	Batch Analyses	√	-
3.2.S.4.5	Justification of Specification	√	√ [7]
3.2.S.5	Reference Standards or Materials	√	-
3.2.S.6	Container Closure System	√	-
3.2.S.7	**Stability**		
3.2.S.7.1	Stability Summary and Conclusions	√	-
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment	√	-
3.2.S.7.3	Stability Data	√	-
3.2.A	**Appendices**		
3.2.A.1	Facilities and Equipment	-	√
3.2.A.2	Adventitious Agents Safety Evaluation	-	√

('**√**' = Accepted / '-' = Not Applicable)

1. A separate QOS for each part (AP / RP), or a single QOS to cover both parts can be provided, deleting all sections of the QOS not relevant to the MF. In cases when a single QOS is provided, the confidential business information/trade secret sections should be clearly identified.
2. A flow chart (including molecular structures and all reagents/solvents) and a short description can be sufficient, if additional detailed information is presented in the Restricted Part. However, for sterile drug substances full validation data on the sterilisation process should be provided in the Applicant's Part (In cases where there is no further sterilisation of the final product).
3. Detailed information
4. Insofar as the information is also relevant for the applicant.
5. Insofar as this information is not relevant for the applicant.
6. Insofar as the information is related to the detailed description of the manufacturing process and the MF Owner sufficiently justifies that there is no need to control these impurities in the final drug substance.
7. Insofar as the information is related to the detailed description of the manufacturing process, control of materials and process validation.

TYPE II – CONTAINER CLOSURE SYSTEM AND COMPONENT MASTER FILES (CCS AND CCC)

The following illustrative examples show how the eCTD structure can be used to present the information on the Container Closure Component (CCC), a CCC Family and/or a Container Closer System (CCS). The Type II MF should be appropriately compiled based on the content and it may be necessary to include additional subsections, which have not been shown in the examples. A MF can contain one or more of the sections shown in the example, as applicable.

EXAMPLE 1 covers a **stoppered glass vial (CCS)**, including each of its CCCs.

The CCCs in this example include three different sizes of the same Type I glass vials and two different types of stoppers with the same dimensions to fit all three vial sizes.

Since the majority of information is common to all three sizes of glass vials, the glass vials can be treated as a CCC Family with their information presented using a single 3.2.S OR 3.2.P section (**choose one format option only**). The unique information to each vial size can be presented under 3.2.S.6 and 3.2.S.7, OR under 3.2.P.7 and 3.2.P.8, depending on which 3.2 structure option is selected.

Since the composition of the stoppers are different, either separate 3.2.S OR 3.2.P sections (**choose one format option only**) should be used for each type of stopper.

Separate 3.2.P sections should also be used for the information on each CCS, due to their stopper differences.

{3.2.S OR 3.2.P sections for the non-product contact CCCs (i.e., the crimping ring and plastic cap) do not need to be included in the MF in this case.}

Figure E-2: Glass Vial (CCC) – Drug Substance Format

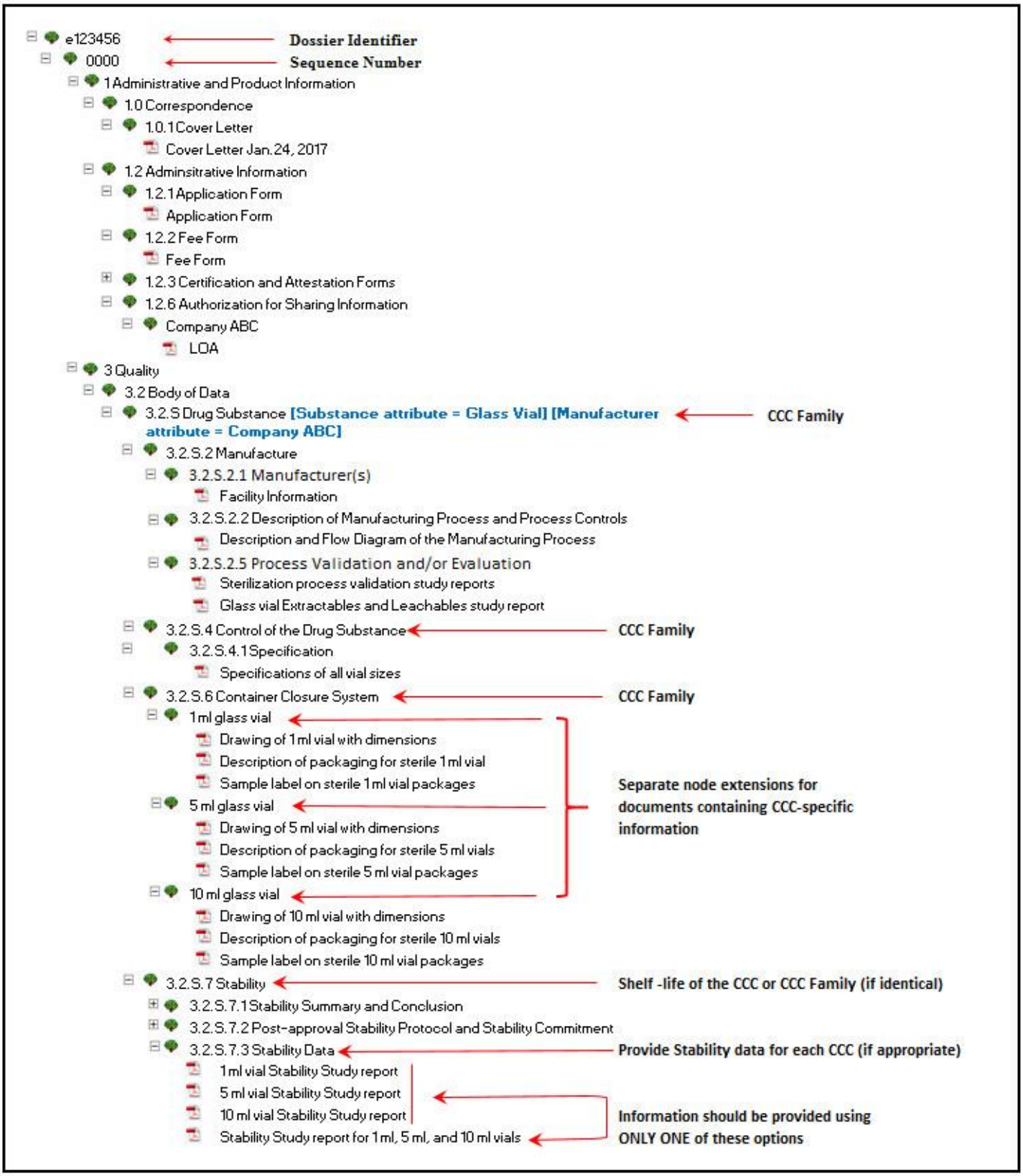


Figure E-3: Glass Vial (CCC) – Drug Product Format

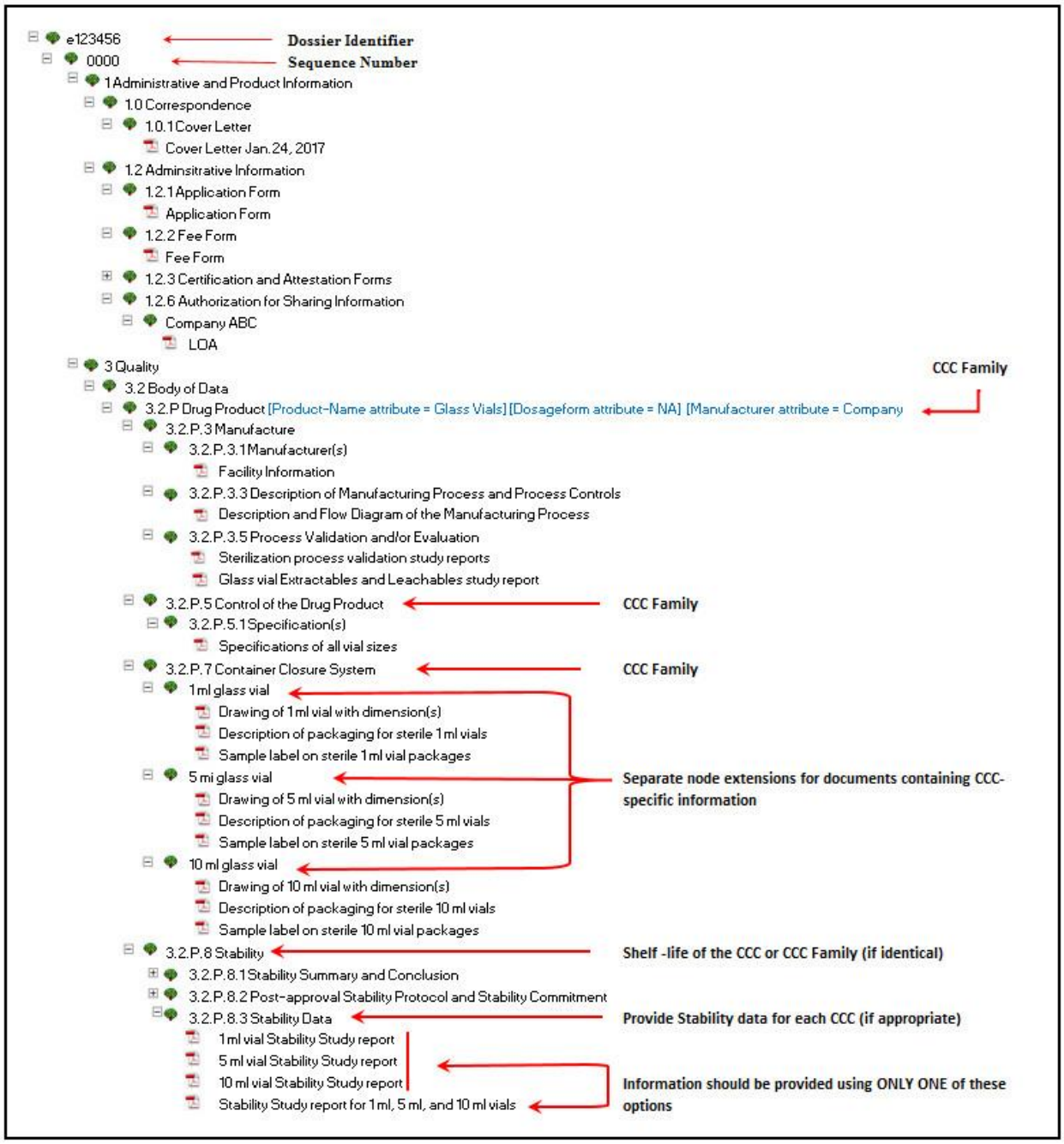
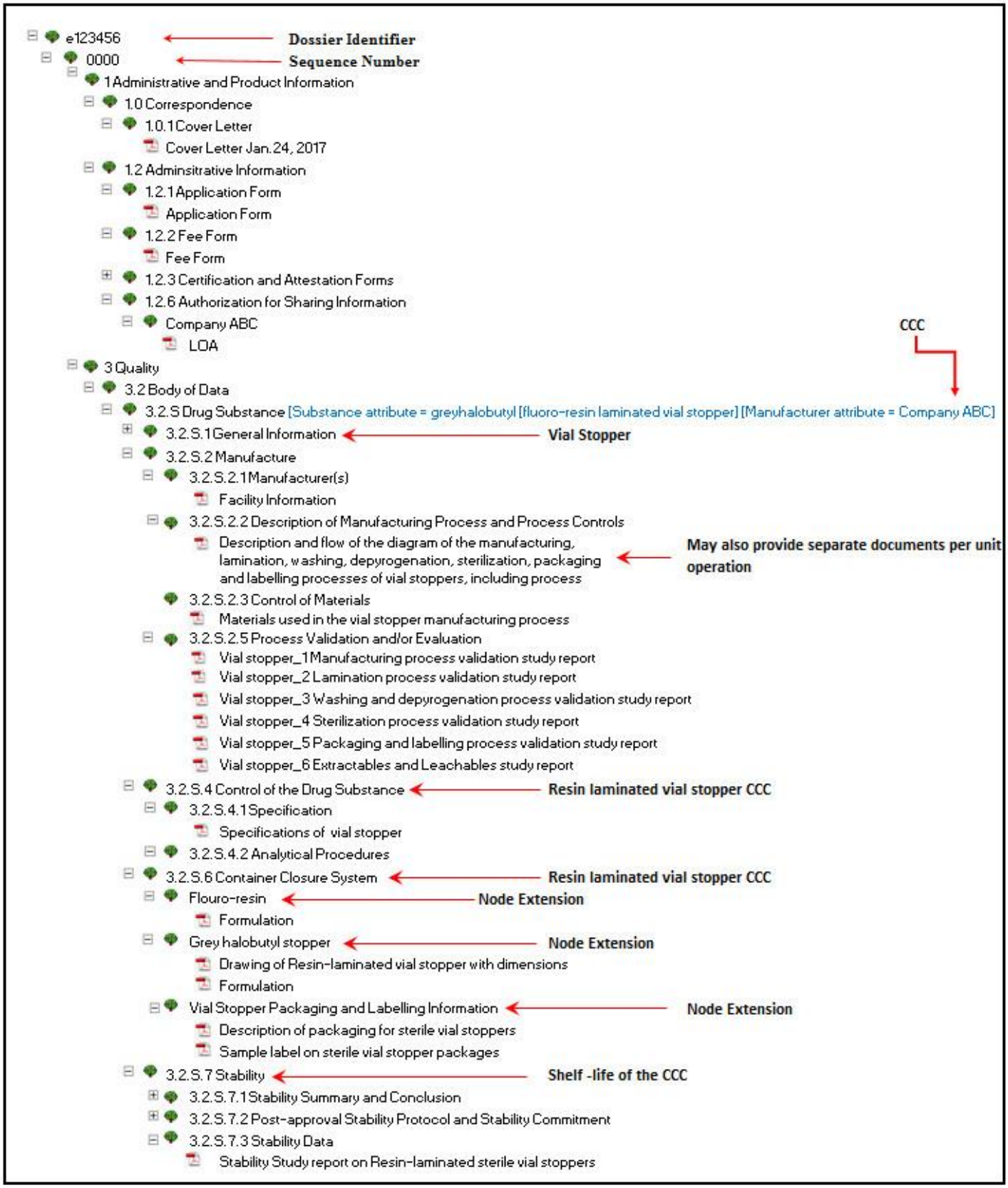
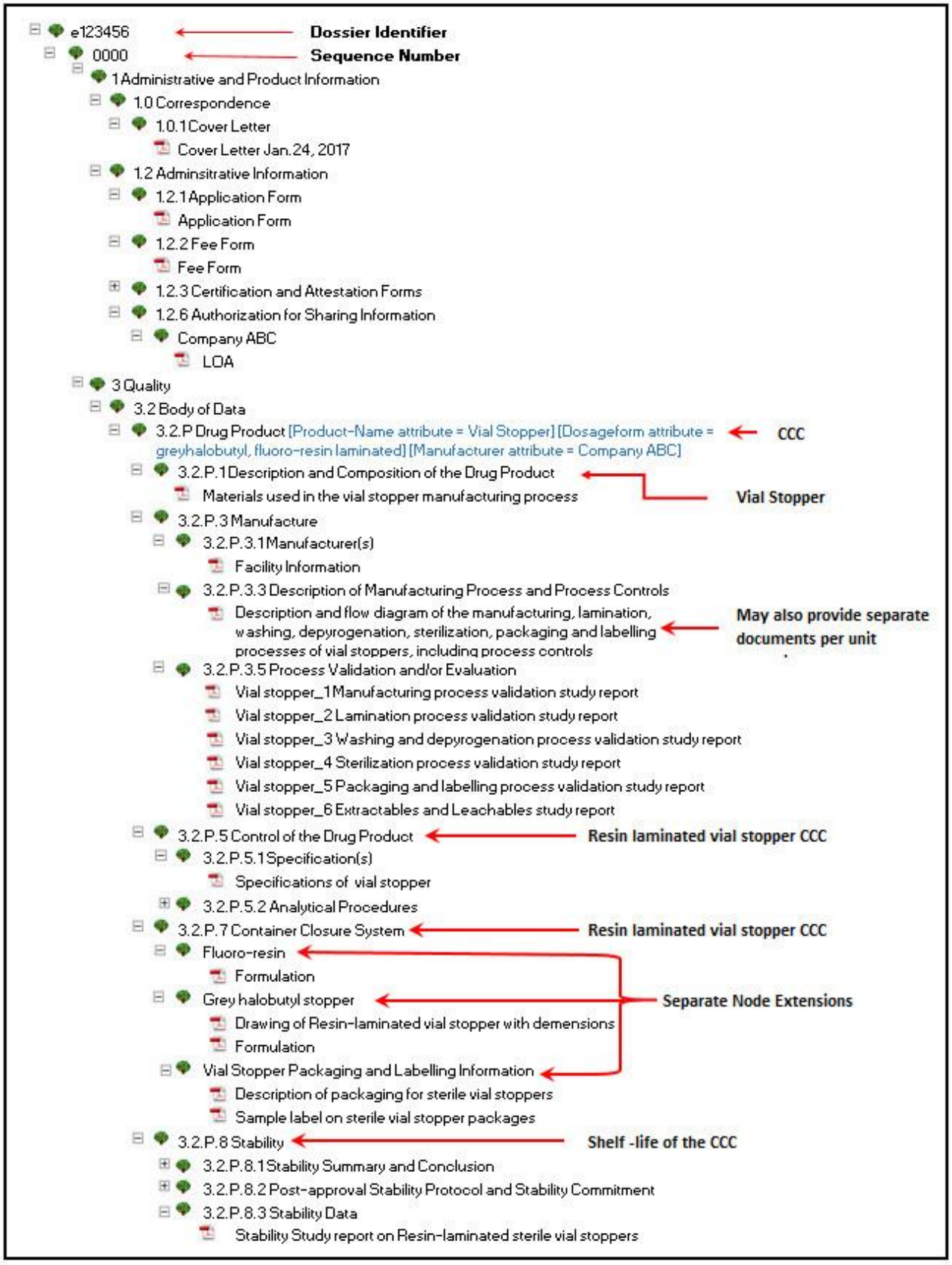


Figure E-4: For the Two Differently Formulated Vial Stoppers (CCC) using either the drug substance (Figure E-4) format OR drug product format (Figure E-5)



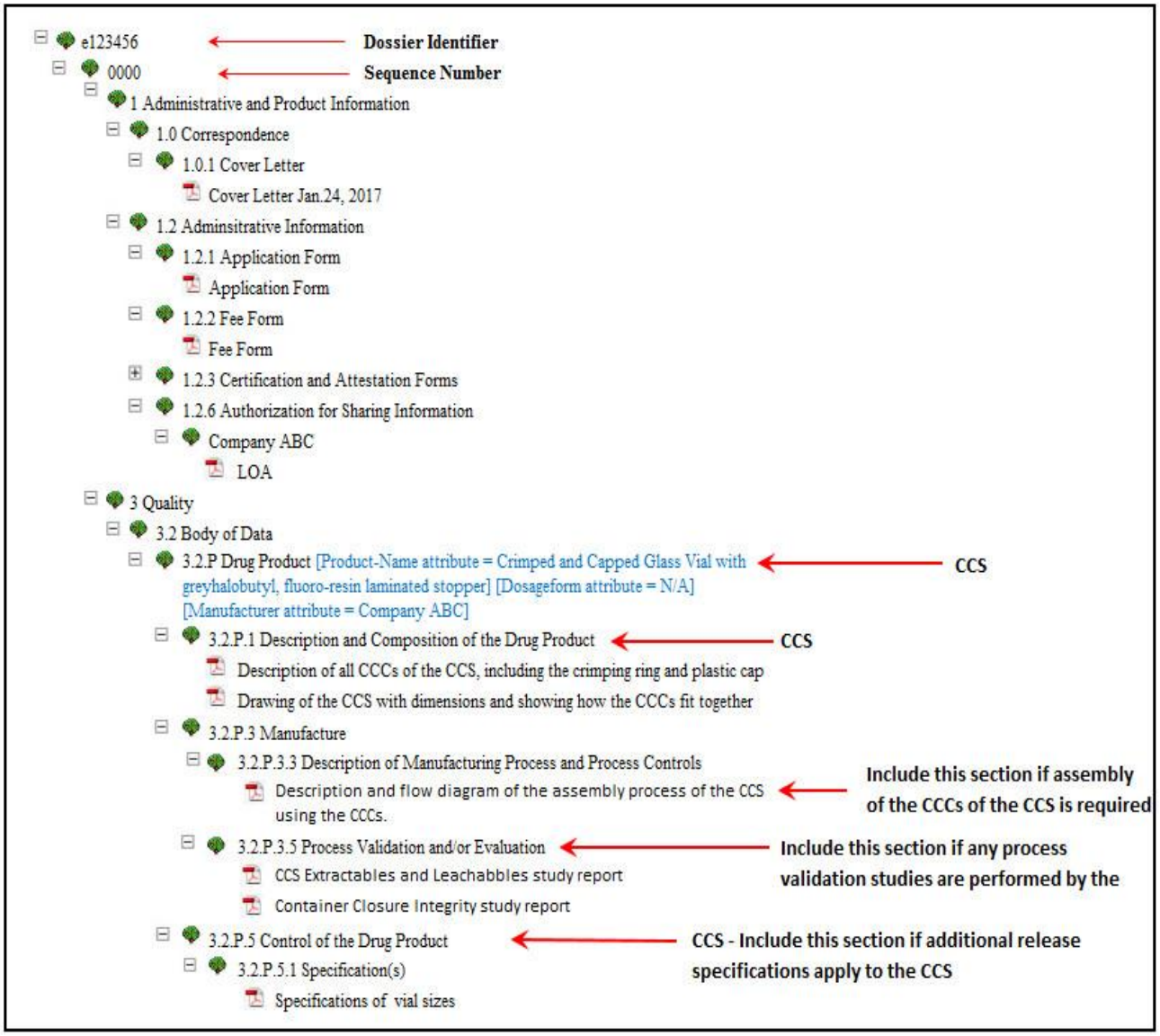
For Rubber Vial Stopper, **3.2.S Drug Substance = CCC [Substance attribute = rubber vial stopper] [Manufacturer attribute = Company ABC],** refer to preceding 3.2.S section (Figure E-4) used to provide information on the greyhalobutyl, fluoro- resin laminated vial stopper, except that in this case, the CCC and information are relevant to the rubber vial stopper.

Figure E-5: Two Differently Formulated Vial Stoppers (CCC) using Drug Product Format



For Rubber Vial Stopper, **3.2.P Drug Product=CCC [Product-Name attribute=vial stopper] [Dosageform attribute= rubber] [Manufacturer attribute= Company ABC]** refer to preceding 3.2.P section (Figure E-5) used to provide information on the greyhalobutyl, fluoro- resin laminated vial stopper, except that in this case, the CCC and information are relevant to the rubber vial stopper.

Figure E-6: Two Container Closure Systems (CCS), each with a Differently Formulated Vial Stopper (CCC)



For a crimped and capped glass vial with a rubber stopper, **3.2.P Drug Product = CCS [Product-Name attribute =Crimped and Capped Glass Vial with rubber stopper] [Dosageform attribute = NA] [Manufacturer attribute = Company ABC],** refer to preceding 3.2.P section (Figure E-6) used to provide information for the CCS, Crimped and Capped Glass Vial with greyhalobutyl, fluoro- resin laminated stopper, except that in this case, the CCS and information are relevant to the Crimped and Capped Glass Vial with rubber vial stopper.

EXAMPLE 2 covers a **syringe** (CCS), including each of its CCCs, namely a: plunger stopper, syringe barrel, plunger rod and syringe needle.

The information on each CCC should be presented using either a separate 3.2.S OR 3.2.P section (**choose one format option only**).

A separate 3.2.P section should be used for the CCS information.
{3.2.S OR 3.2.P sections for the non-product contact CCCs (i.e., the flange extender and needle shield) do not need to be included in the MF in this case.}

Figure E-7: Plunger Stopper Container Closure Component (CCC) – Drug Substance Format

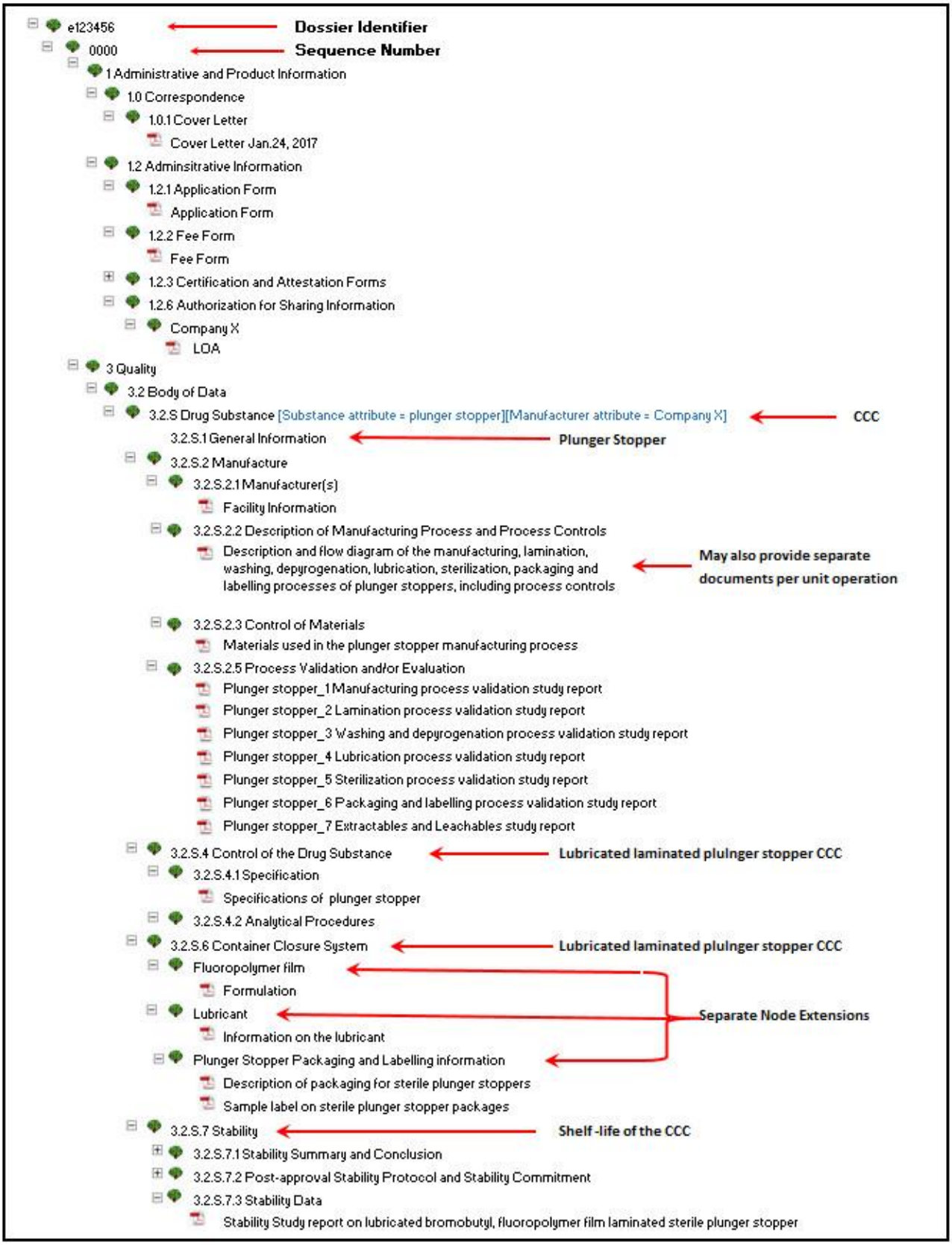


Figure E-8: Plunger Stopper Container Closure Component (CCC) – Drug Product Format

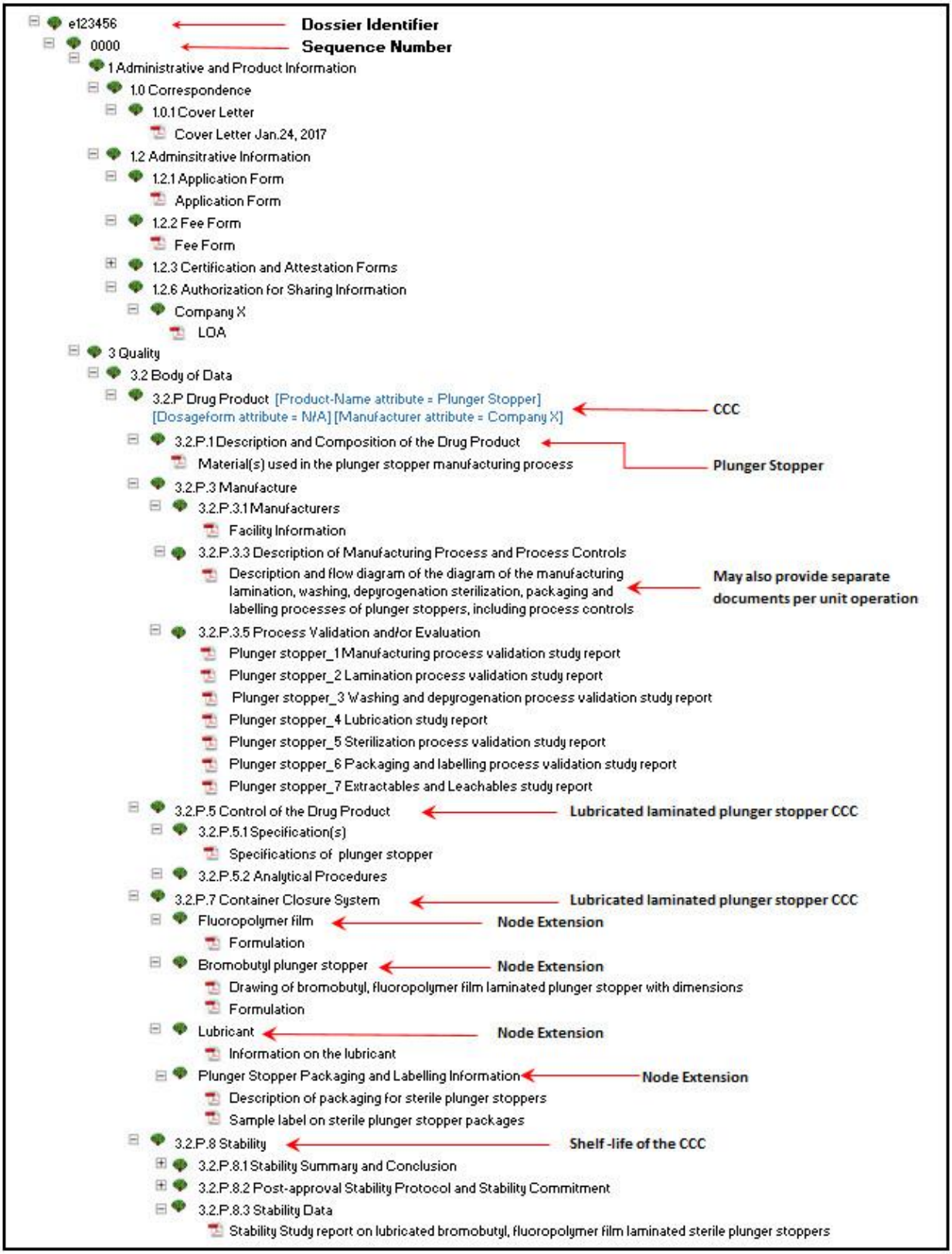


Figure E-9: Syringe Barrel Container Closure Component (CCC) using Drug Substance Format

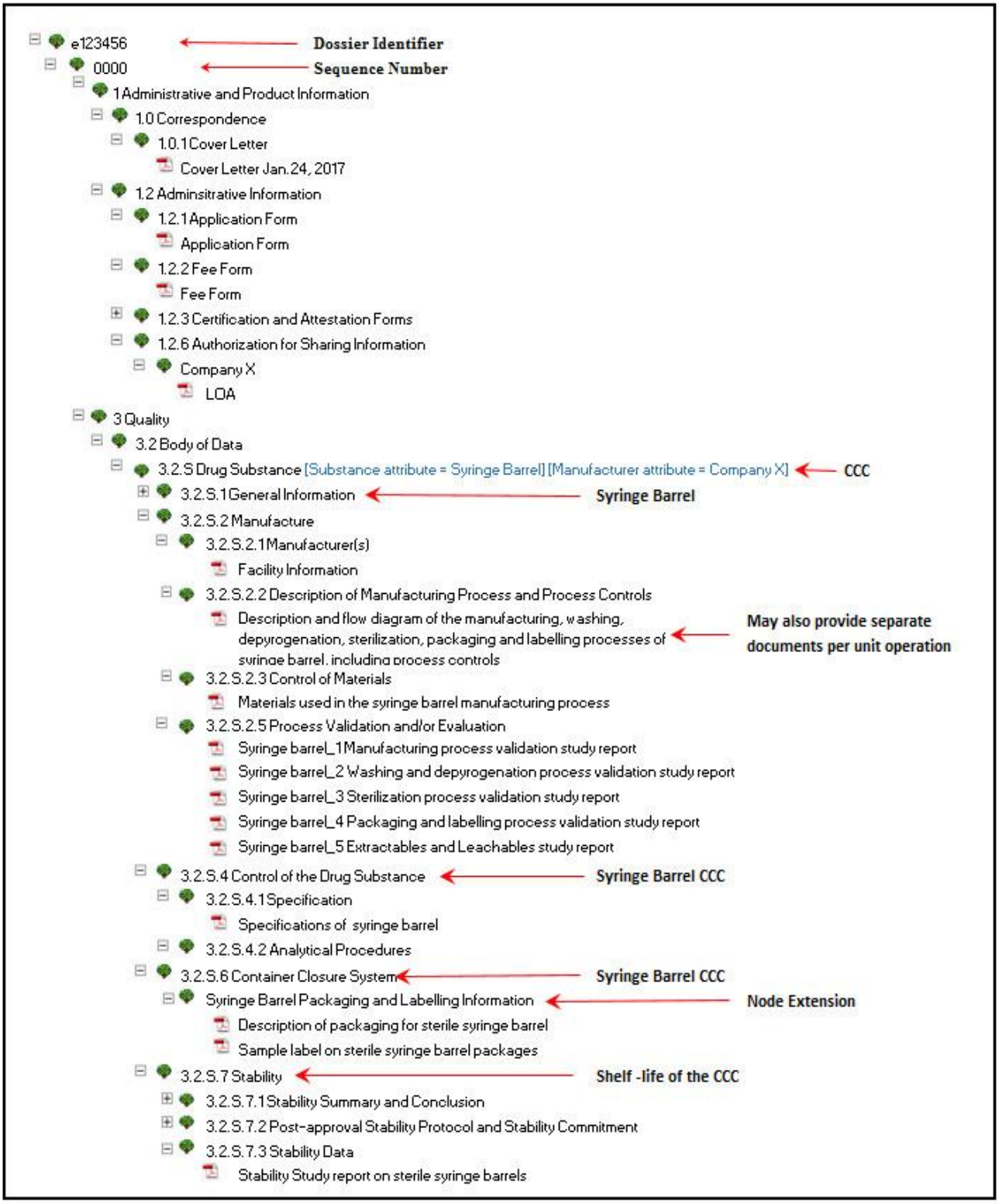


Figure E-10: Syringe Barrel Container Closure Component (CCC) using Drug Product Format

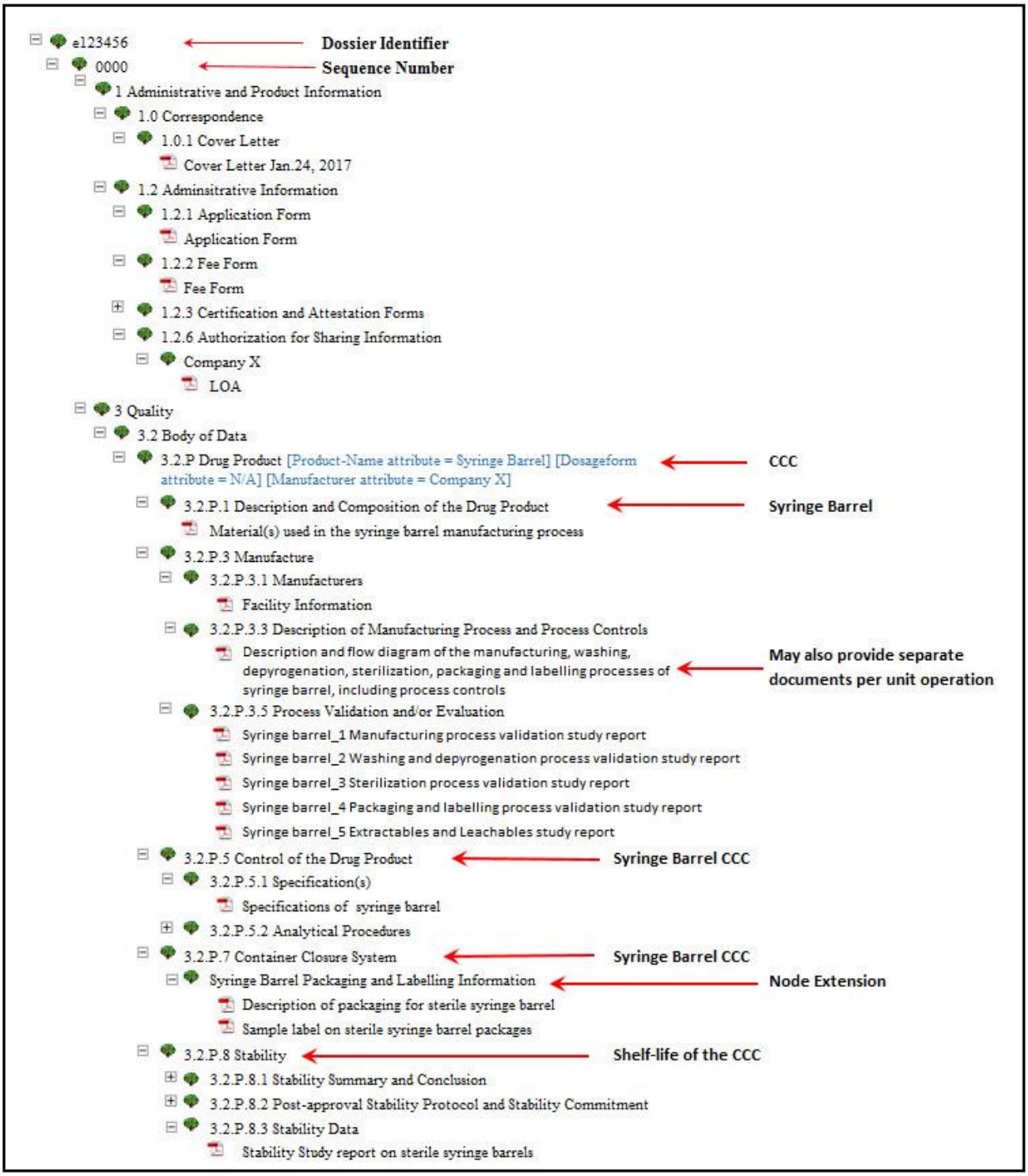


Figure E-11: Plunger Rod Container Closure Component (CCC) Using Drug Substance Format

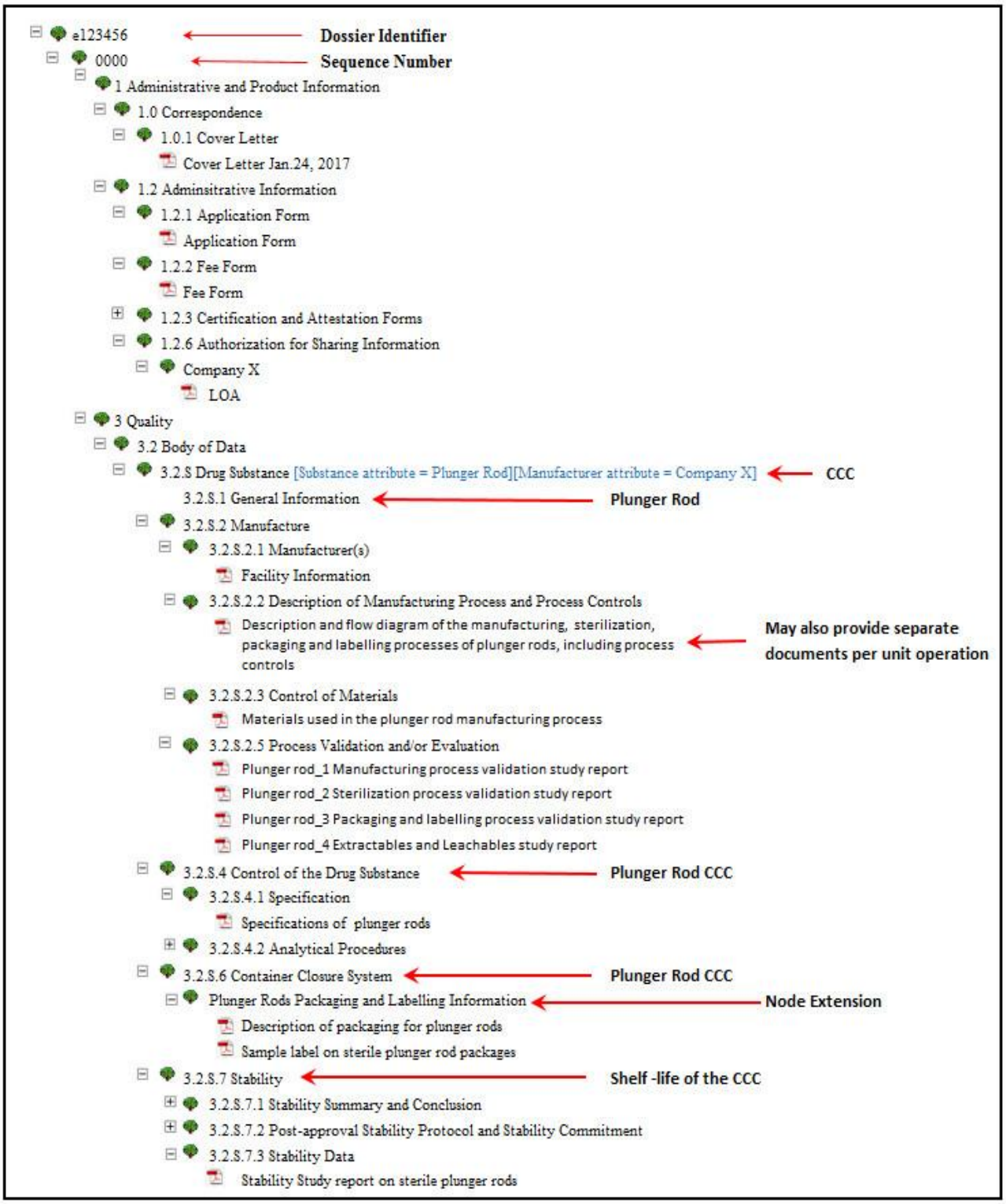


Figure E-12: Plunger Rod Container Closure Component (CCC) Using Drug Product Format

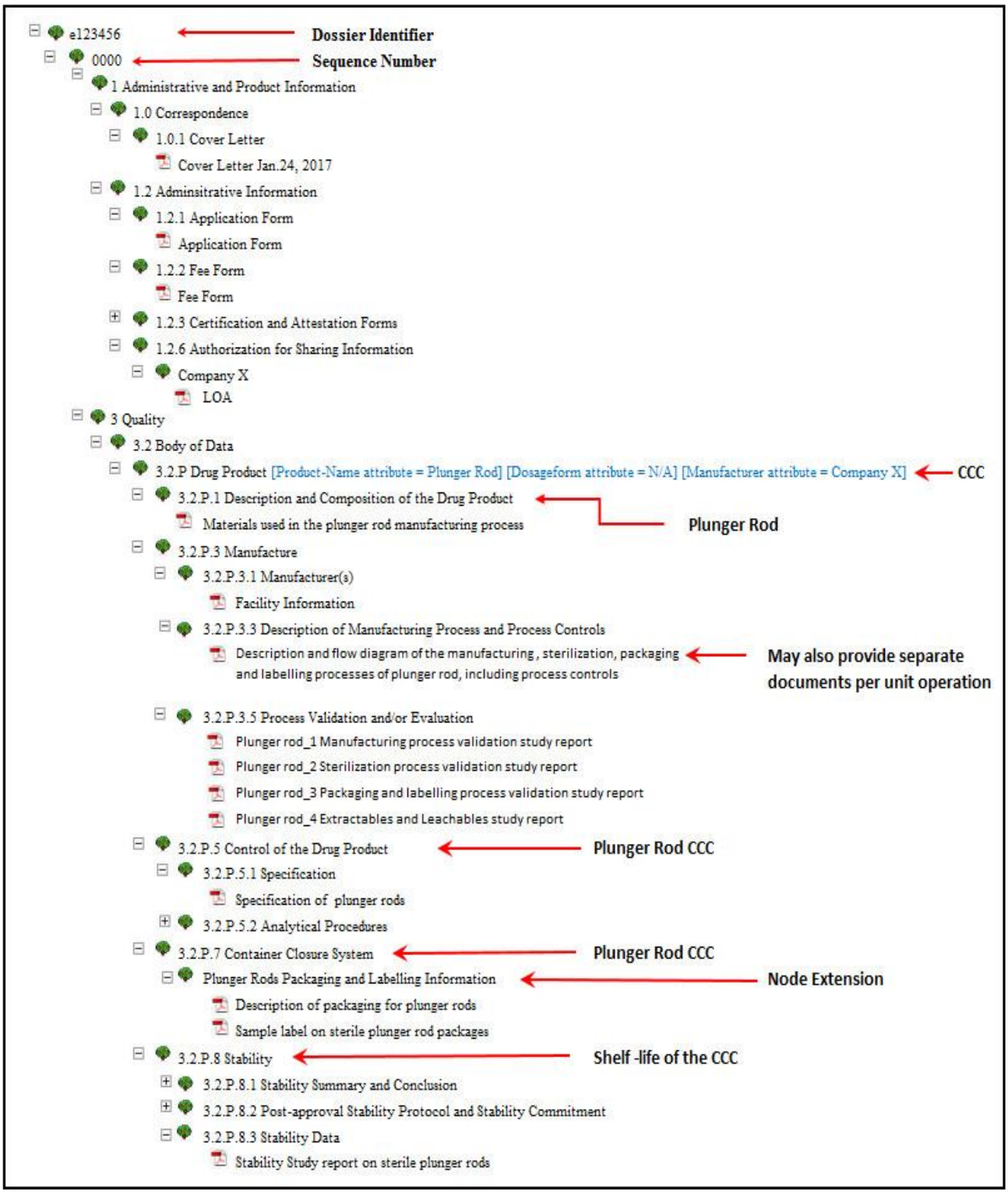


Figure E-13: Syringe Needle Container Closure Component (CCC) using Drug Substance Format

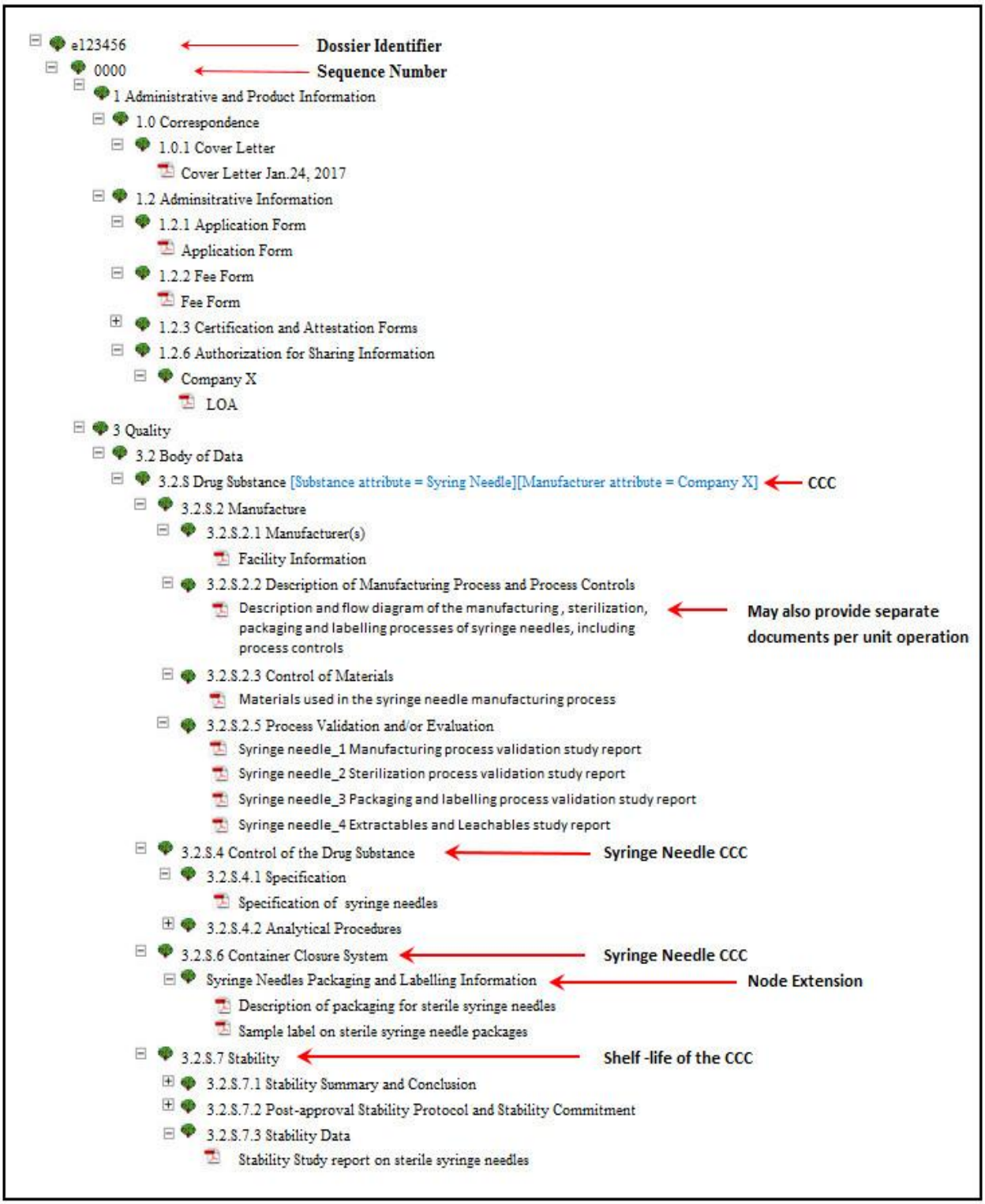


Figure E-14: Syringe Needle Container Closure Component (CCC) using Drug Product Format

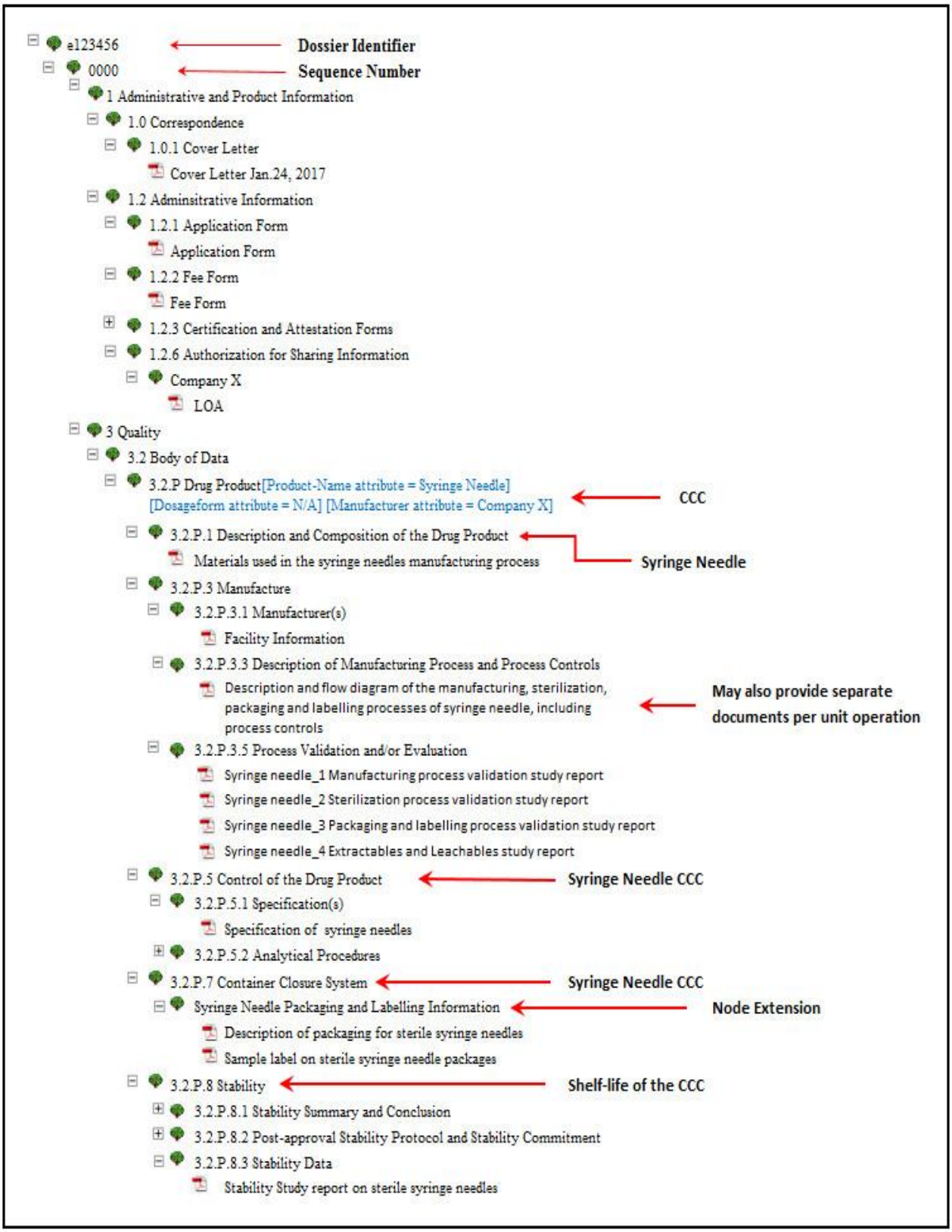
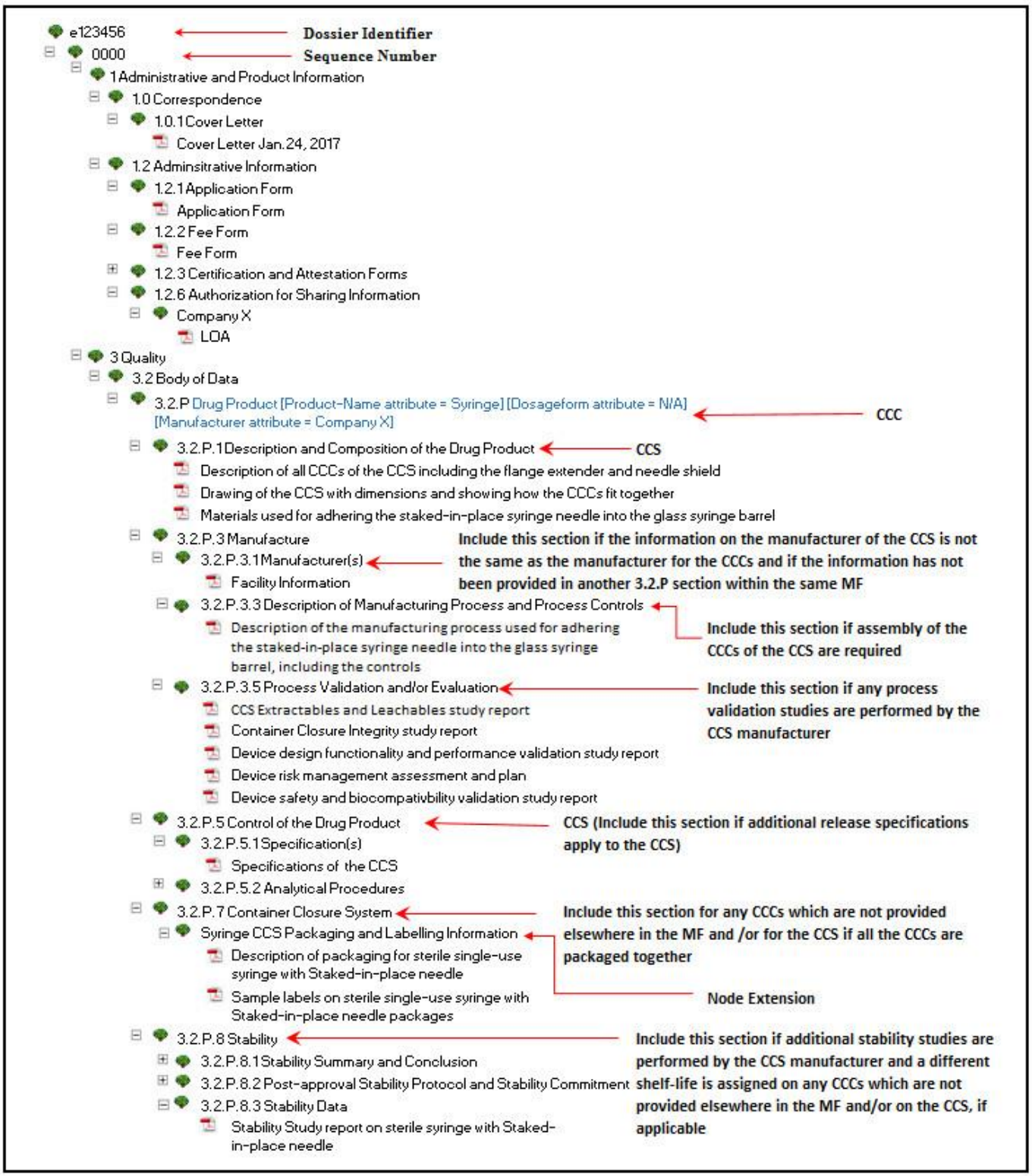


Figure E-15: Syringe Container Closure System (CCS) using Drug Product Format



TYPE III – EXCIPIENT MASTER FILES

The following three illustrative examples show how the eCTD folder structure can be used to present the information on a single ingredient excipient, a multi-ingredient excipient and an excipient Family. A Type III MF should be appropriately compiled based on the content and it may be necessary to include additional subsections and/or Modules (e.g., toxicological information in Module 4) which have not been shown in the examples. An MF can contain one or more of the sections shown in the examples, as applicable.

EXAMPLE 1: Using a separate 3.2.S OR 3.2.P section (**choose one format option only**) for each single ingredient excipient or each excipient Family:

The relevant 3.2.S OR 3.2.P subsections should be used for the information on each single ingredient excipient or excipient family.

Figure E-16: Single Ingredient Excipient(s) and/or Excipient Family (Families) using 3.2.S Drug Substance Format

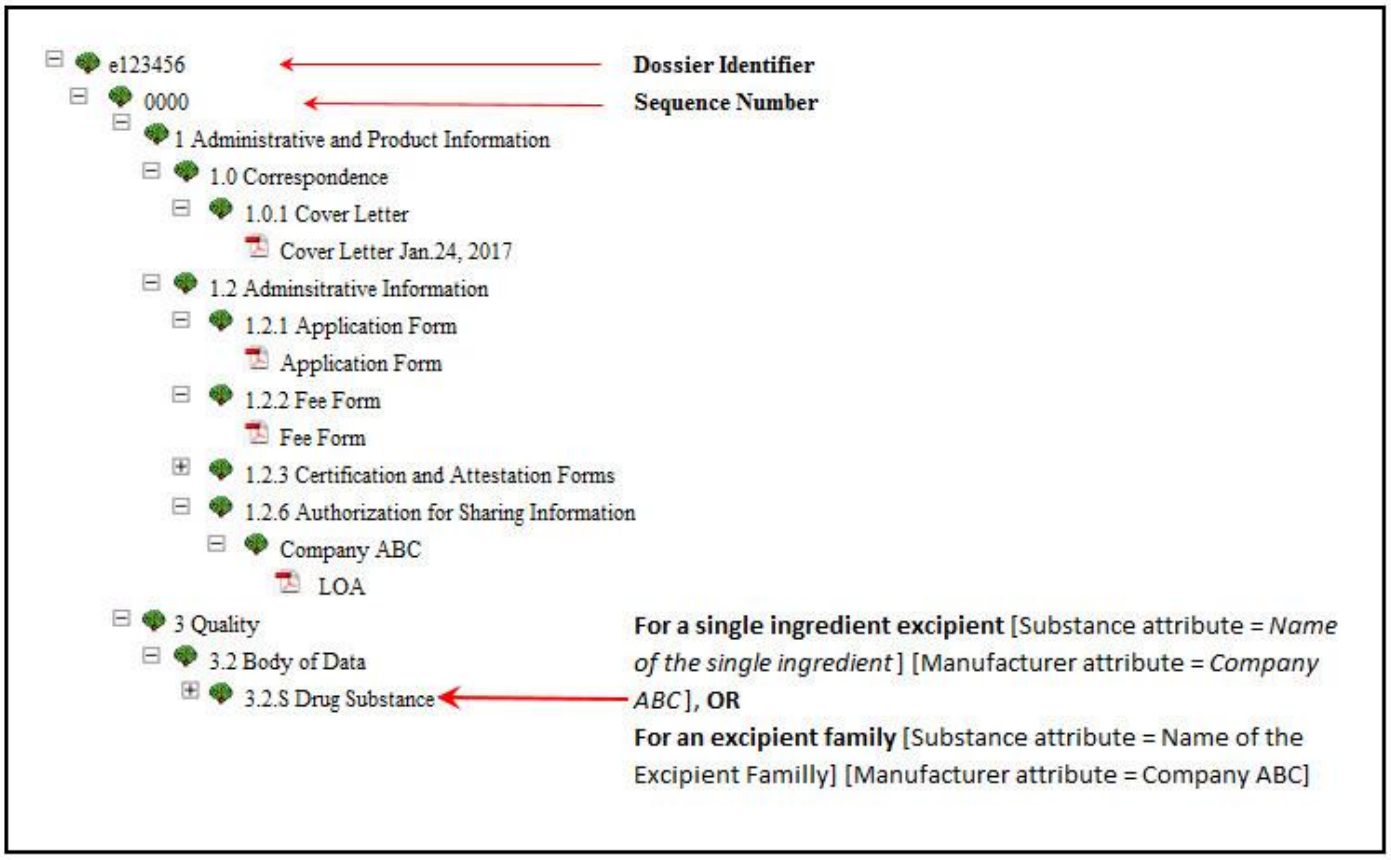
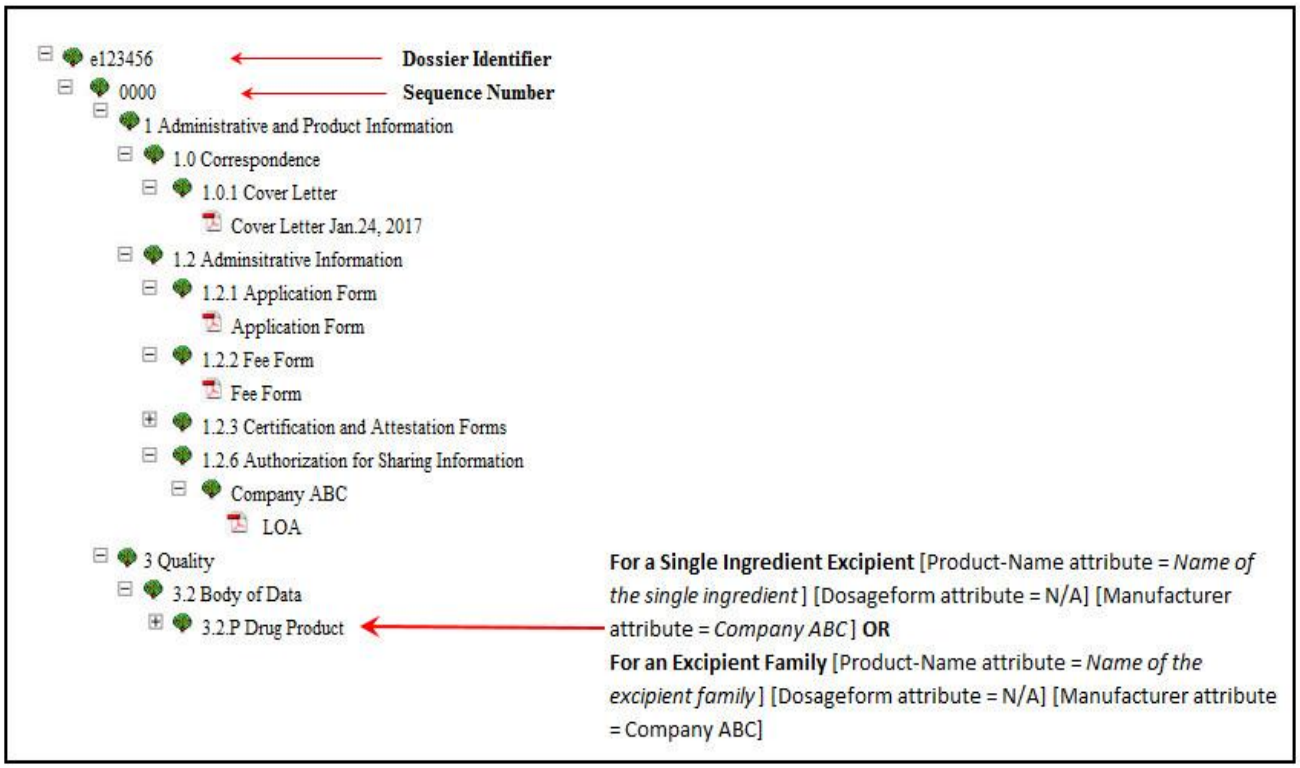
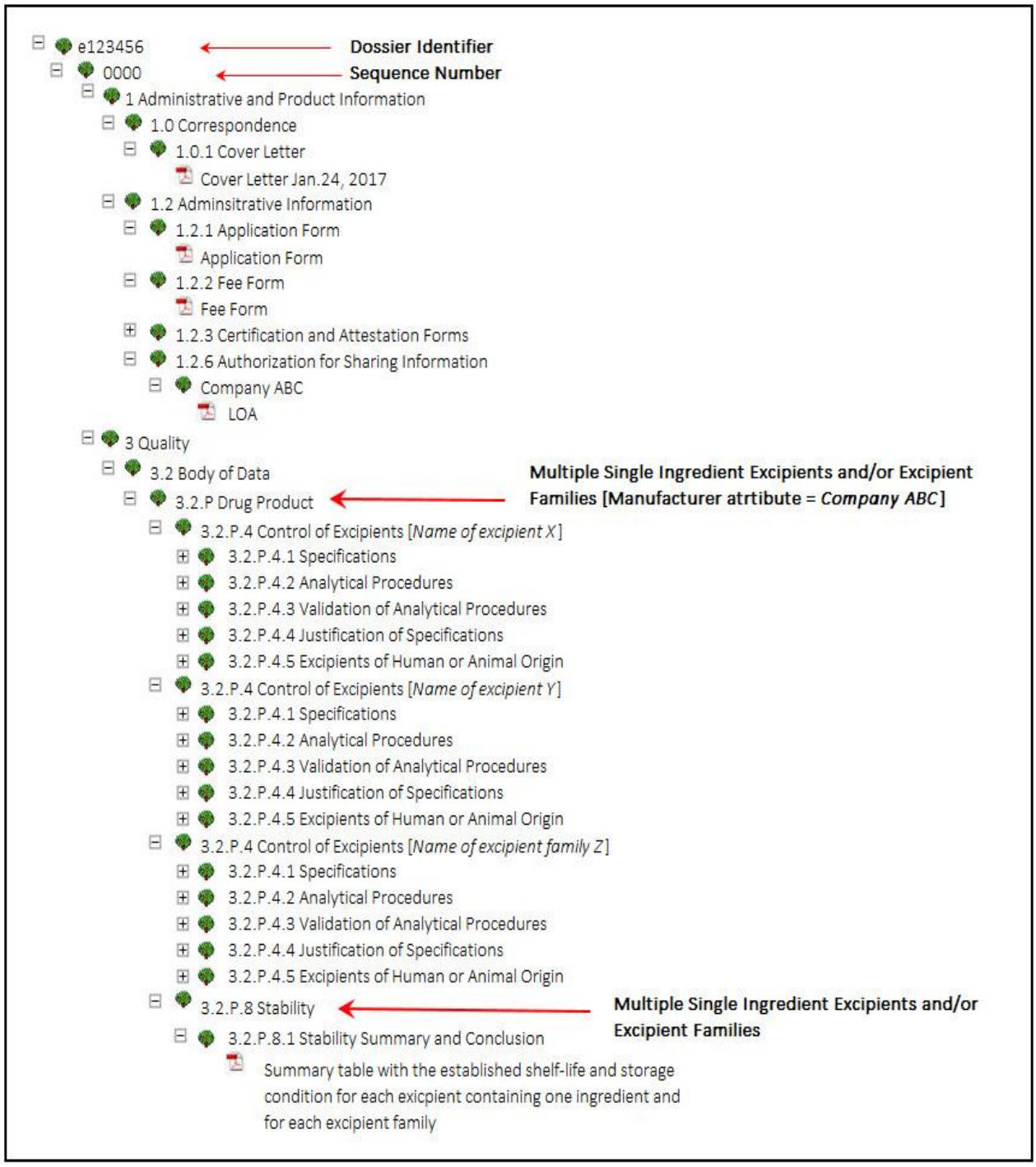


Figure E-17: Single Ingredient Excipient(s) and/or Excipient Family (Families) using 3.2.P Drug Product Format



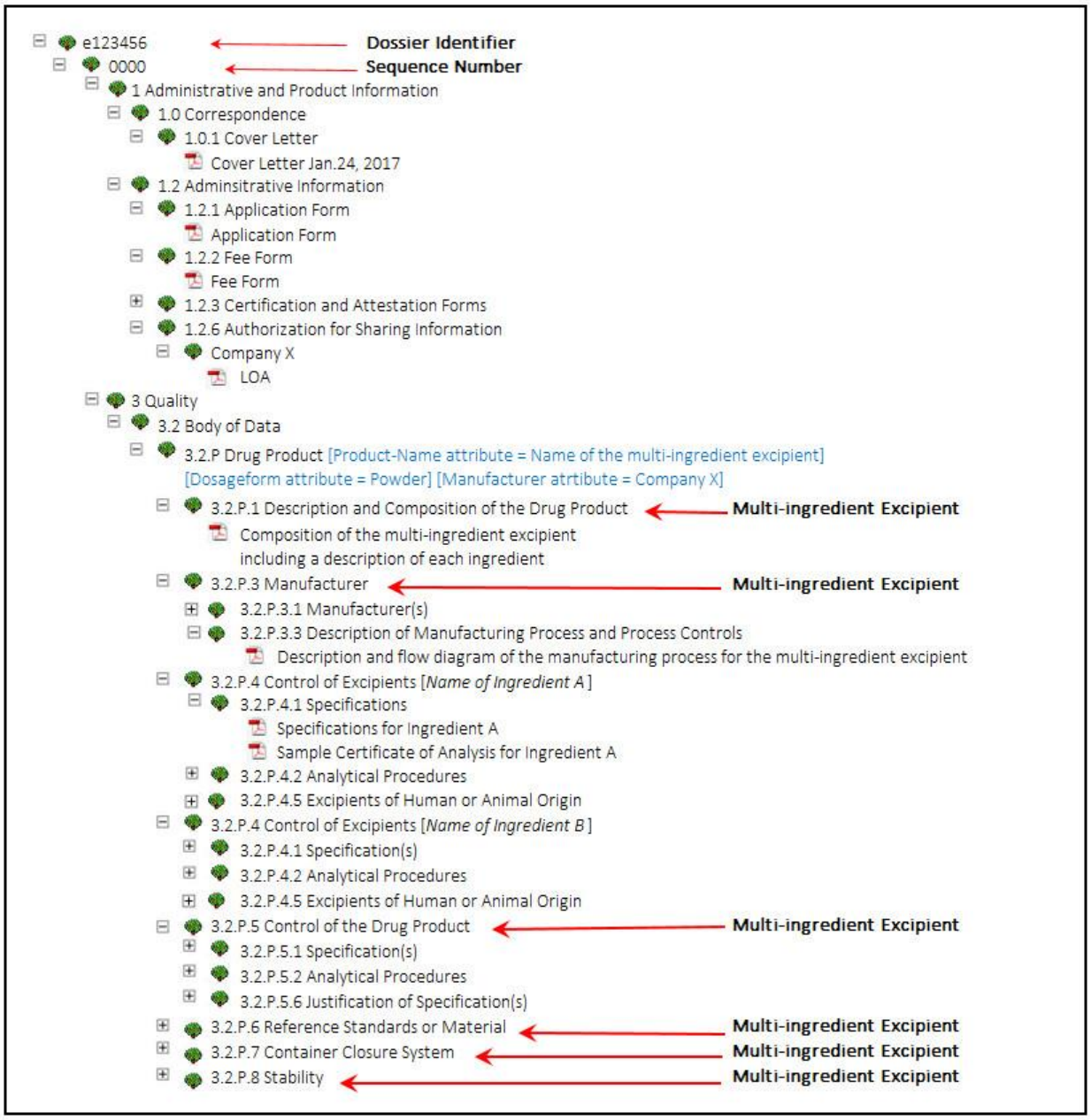
EXAMPLE 2: Using one 3.2.P section containing separate 3.2.P.4 subsections for each single ingredient excipient or each excipient family. **Irrelevant attributes** at the 3.2.P level can be excluded in this case.

Figure E-18: Single Ingredient Excipient(s) and/or Excipient Family (Families) using 3.2.P.4 Control of Excipients Format



EXAMPLE 3: Using a separate 3.2.P section for each multi-ingredient excipient including separate 3.2.P.4 subsections for each ingredient contained within that excipient:

Figure E-19: Multi-ingredient Excipients using Drug Product Format



For the subsequent excipient, a repeating 3.2.P section can be used, for example: 3.2.P Drug Product [Product-Name attribute= Name of the multi-ingredient excipient][Dosageform attribute= Solution][Manufacturer attribute= Company X]. Refer to the preceding 3.2.P section (Figure E-19) used to provide information for the excipient in powder dosage form, except in this case, information is relevant to the excipient in solution dosage form.

TYPE IV – DRUG PRODUCT MASTER FILES

1. All documents in this folder will be considered Restricted Part (RP) of the MF.
2. Two separate documents should be submitted in the folder "2.3 Quality Overall Summary", a "QOS (RP)" and a "QOS (AP)" files.

Figure E-20: MF Type IV - Drug Product

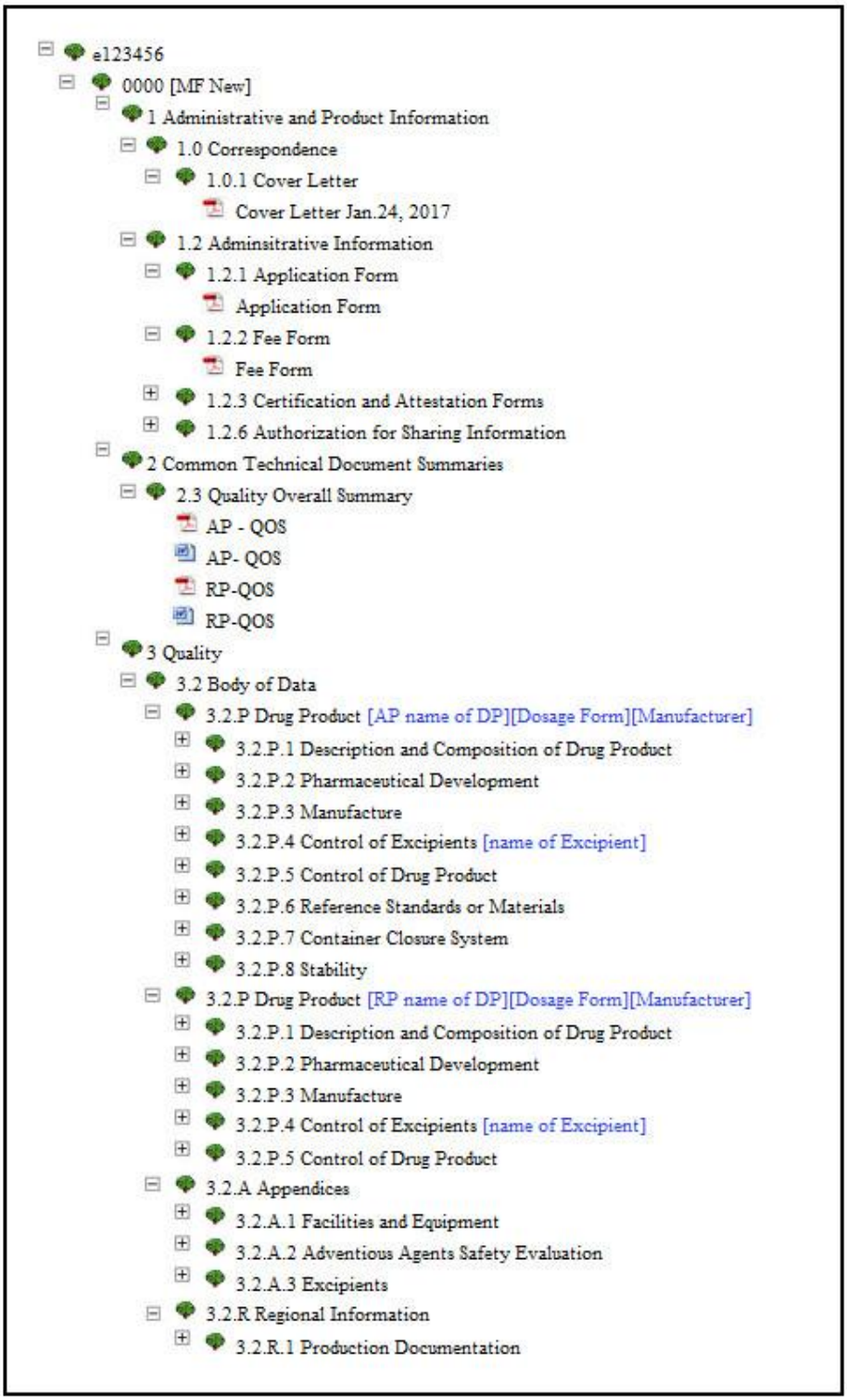


Table E-2: Distribution of MF Information between the Applicant and Restricted Parts for Type IV - Drug Products Master Files

Module/Folder Names		Proposed 2015 Applicant's Part	Proposed 2015 Restricted Part
Module 1: Administrative and Product Information			
1.0	**Correspondence**		
1.0.1	Cover Letter	-	√
1.0.2	Life Cycle Management Table (Only required for eCTD)	-	√
1.0.3	Copy of Health Canada Issued Correspondence	-	√
1.0.4	Health Canada Solicited Information	-	√
1.0.7	General Note to Reviewer	-	√
1.1	**Table of Contents** (Only required for non-eCTD))		
1.2	**Administrative Information**		
1.2.1	Application Forms	-	√
1.2.2	Fee Forms MF Application/Amendment Fee Form	-	√
1.2.3	Certification and Attestation Forms	-	√
1.2.5	**Compliance and Site Information**		
1.2.5.2	Establishment Licensing	-	√
1.2.5.5	Good Manufacturing Practices	-	√
1.2.6	Authorization for Sharing Information	-	√
1.2.7	International Information	-	√
1.3	**Product Information**		
1.3.6	Certified Product Information Document	-	√
Module 2: Common Technical Document Summary			
2.3	Quality Overall Summary (QOS)[1]	√	√
Module 3: Quality			
3.1	Table of Contents of Module 3 (Not required for eCTD)	√	√
3.2	**Body of Data**		
3.2.P	**Drug Product**		
3.2.P.1	Description and Composition of the Drug Product	√	√ [3]
3.2.P.2	Pharmaceutical Development	√ [4]	√ [3]
3.2.P.2.1	Components of the Drug Product*	√ [5]	√
3.2.P.2.2	Drug Product*	-	√
3.2.P.2.3	Manufacturing Process Development*	-	√
3.2.P.2.4	Container Closure System*	-	√
3.2.P.2.5	Microbiological Attributes*	-	√
3.2.P.2.6	Compatibility*	-	√

Module/Folder Names		Proposed 2015 Applicant's Part	Proposed 2015 Restricted Part
3.2.P.3	**Manufacture**		
3.2.P.3.1	Manufacturer(s)	√	√
3.2.P.3.2	Batch Formula	√	√
3.2.P.3.3	Description of Manufacturing Process and Process Controls	√ [2]	√ [3]
3.2.P.3.4	Controls of Critical Steps and Intermediates	√ [4]	√ [6]
3.2.P.3.5	Process Validation and /or Evaluation	-	√
3.2.P.4	Control of Excipients	√ [4]	√ [6]
3.2.P.4.1	Specifications	-	√
3.2.P.4.2	Analytical Procedures	-	√
3.2.P.4.3	Validation of Analytical Procedures	-	√
3.2.P.4.4	Justification of Specifications	-	√
3.2.P.4.5	Excipients of Human or Animal Origin	-	√
3.2.P.4.6	Novel Excipients	-	√
3.2.P.5	**Control of Drug Product**		
3.2.P.5.1	Specifications	√	-
3.2.P.5.2	Analytical Procedures	√	-
3.2.P.5.3	Validation of Analytical Procedures	√	-
3.2.P.5.4	Batch Analyses	√	-
3.2.P.5.5	Characterisation of Impurities	√	√ [7]
3.2.P.5.6	Justification of Specifications	√	√ [8]
3.2.P.6	Reference Standards or Materials	√	-
3.2.P.7	Container Closer System	√	-
3.2.P.8	**Stability**		
3.2.P.8.1	Stability Summary and Conclusions	√	-
3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment	√	-
3.2.P.8.3	Stability Data	√	-
3.2.A	**Appendices**		
3.2.A.1	Facilities and Equipment	-	√
3.2.A.2	Adventitious Agents Safety Evaluation	-	√
3.2.A.3	Excipients	-	√
3.2.R	**Regional Information**		
3.2.R.1	Production Documentation	-	√

('**√**' = Accepted / '-' = Not Applicable)

1. A separate QOS for each part (AP / RP) or a single QOS to cover both parts can be provided, deleting all sections of the QOS not relevant to the MF. In cases when a single QOS is provided, the confidential business information/trade secret sections should be clearly identified.
2. A flow chart (including all manufacturing steps, excipients and processing agents) and a short description can be sufficient, if additional detailed information is presented in the Restricted Part.

3. Detailed information.
4. Insofar as the information is also relevant for the applicant.
5. Complete qualitative composition is provided to the applicant.
6. Insofar as this information is not relevant for the applicant.
7. Insofar as the information is related to the detailed description of the manufacturing process and the MF Owner sufficiently justifies that there is no need to control these impurities in the final drug product.
8. Insofar as the information is related to the detailed description of the manufacturing process, control of materials and process validation.

Appendix F: Undefined Regulatory Activity (UDRA)

The UDRA regulatory activity type should be used when there is no relevant regulatory activity defined in the Management of Drug Submission and Applications that can be used. A list of regulatory transactions that can be used for the UDRA activity type is provided in the Transaction Description document available on the Filing Submissions Electronically information page. Any other use of this regulatory activity type should be discussed with Health Canada prior to filing.

Table F-1: Regulatory transaction descriptions for UDRAs

Regulatory Transaction Description	When to use the description
Response to Advisement Letter to update the Product Monograph	Rationale to not incorporate changes requested via advisement letter (mandatory in eCTD format)
Notification of Discontinued Sale	When intending to cancel a DIN (recommended in eCTD format)
Notification on Drug Shortage	When notifying Health Canada about a drug shortage, including a request for Special Lot Release related to the drug shortage
Advance notification of safety or efficacy issue raised by company or other regulator	Immediate notification of updates to labelling and/or risk communications made in, or requested by other jurisdictions. (mandatory in eCTD format)
Quality issue raised by company and/or other regulator	Quality related issues
GMP compliance issue raised by other regulators	Issues/concerns with media fill failures, sterility, violation of GMPs, out of specifications results (e.g. failure of appearance test due to visible particles), potency assay, stability, etc. which are not subject submission filing.
Safety Information related to published literature	Information for published literature
Reclassification request under BGTD Lot Release Program	When submitting outside of a regulatory activity
Annual updates on NOC/c commitments	When submitting just a cover letter to provide information to Health Canada, i.e., annual updates on NOC/c commitments, • Information related to ongoing confirmatory trials (i.e. updates, status, progress reports, delays, etc.) • Annual progress report for ongoing trials • Something requested in a Letter of Undertaking (LOU) that does not result from confirmatory trials, and does not impact the Product Monograph (PM)