Health Canada Santé Canada

September 7, 2012

Notice

Our file number: 12-115151-181

Re: Guidance Document: Creation of the Canadian Module 1 Backbone

Health Canada is pleased to announce the finalization of the *Guidance Document: Creation of the Canadian Module 1 Backbone* as a result of a 30 day consultation period. This document replaces the 2004 *Guidance for Industry: Creation of the Canadian Module 1 eCTD Backbone File.*

This guidance document outlines the creation of a regional backbone file according to the Canadian Module 1 schema. The Canadian Module 1 Schema files are to be used in the preparation and filing of drug regulatory activities in the electronic Common Technical Document (eCTD) format established by the International Conference on Harmonisation (ICH).

This guidance document is meant be read in conjunction with the:

- *Canadian Module 1 Schema Version 2.2*; and
- *Draft Guidance for Industry: Preparation of Drug Regulatory Activities in Electronic Common Technical Document (eCTD) Format.*

It should be noted that, although Clinical Trial Applications (CTA) and Drug Master Files (DMFs) are included in the schema, they are not yet accepted in the eCTD format. Please consult the *Guidance for Industry: Preparation of Drug Regulatory Activities in Electronic Common Technical Document (eCTD) Format* as well as the most recently published notices regarding eCTD regulatory activities to verify the scope of regulatory activities accepted in the eCTD format.

At this time Health Canada implementation is as per the following schedule:

- As of September 30th, 2012, Health Canada will be accepting regulatory activities built using the revised *Canadian Module 1 Schema Version 2.2.*
- As of March 31st, 2013, Health Canada will no longer be accepting regulatory activities built with the old Canadian Module 1 DTD.

…/2

Questions and comments relating to this document should be submitted, preferably in electronic format, to:

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Health Canada Santé Canada

GUIDANCE DOCUMENT
Creation of the Canadian Module 1 Backbone

Published by authority of the
Minister of Health

Date Adopted	2004/06/15
Revised Date	2012/08/03
Effective Date	2012/09/30

Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's (HPFB) mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for products and food; and • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

Également disponible en français sous le titre : Ligne directrice : Création du fichier de base du module 1 canadien

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

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 scientific 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 guidance, 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.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1 INTRODUCTION

1.1 Policy Objective

To ensure sponsors have access to all the information needed to provide a drug dossier to Health Canada in electronic Common Technical Document (eCTD) format.

1.2 Policy Statement

This guidance document outlines the creation of a regional backbone file according to the Canadian Module 1 schema. This backbone file is to be used in the preparation and filing of drug regulatory transactions in eCTD format established by the International Conference on Harmonisation (ICH).

1.3 Scope and Application

This Guidance document applies to all regulatory activities being provided to Health Canada in eCTD format. This guidance document is meant to be read in conjunction with the documents listed in Appendix A, "References".

1.4 Background

The original Canadian Module 1 DTD (v1.0) was released in May 2004, well before Health Canada began receiving large numbers of regulatory activities in eCTD format. Since that time, both industry and Health Canada have learned much about using the eCTD format. Health Canada has also revised the Module 1 structure in the CTD format, and would now like to apply these revisions to the Module 1 (m1) specifications. Given the desire to adopt the eCTD v4.0 / Regulated Product Submissions (RPS) in the foreseeable future, the decision has been made to move to a World Wide Web Consortium (W3C) Schema approach to define the updated M1 as outlined in the *Guidance for Industry: Preparation of Drug Regulatory Activities in eCTD Format*.

It is understood that this will not be the last time that the m1 specification will change. It is expected that further work in this area will be required; however it should be noted that any future changes will be accompanied by a well thought out introduction to minimize the impact on industry (introduced at scheduled interval to allow stability).

2 PREPARING THE CANADIAN MODULE 1 BACKBONE FILE

The Canadian Module 1 eCTD backbone file comprises three main components:

- A fixed 'eXtensible Markup Language' (XML) Declaration;
- The eCTD Regulatory Transaction Information (metadata); and
- The eCTD Table of Contents describing the actual files provided.

2.1 Creating the Module 1 electronic Common Technical Document (eCTD) Backbone File for a Given Regulatory Transaction (Sequence)

To create the Canadian Module 1 backbone file for a given regulatory transaction:

1. Create an XML file with the appropriate XML declaration using an authenticated eCTD preparation software. See "Preparing the XML Declaration" below.
2. Create an `<ectd-regulatory-transaction-information>` element containing the appropriate metadata values describing this regulatory transaction. See "Preparing the eCTD Regulatory Transaction Information" below.
3. Create an `<m1-administrative-and-product-information>` element containing additional elements as needed for this regulatory transaction, as described in "Preparing the eCTD Table of Contents" below. These elements will be of two broad types:
    - Heading elements, organizing the content in the Module 1 to meet Health Canada's review requirements.
    - Leaf elements, providing a file system reference to each file being submitted in the regulatory transaction as part of Module 1, along with other information such as eCTD check-sum and life-cycle information.
4. Name the Canadian Module 1 eCTD backbone file "ca-regional.xml" and place it in the "ca" subfolder within the Module 1 ("m1") subfolder of the regulatory transaction.
5. Validate the resulting backbone using a suitable eCTD Validation tool.

3 PREPARING THE EXTENSIBLE MARKUP LANGUAGE (XML) DECLARATION

All Canadian Module 1 backbone files prepared for Health Canada will contain the standard XML declaration as illustrated in Figure 1 below. Note that the required text includes both line 1 (identifying the file as an XML file) and the root element `<hcsc_ectd>` on line 2 with its attributes linking this XML file to the XML definition prepared by Health Canada.

```
1    <?xml version="1.0" encoding="utf-8"?>
2    <hcsc_ectd schema-version="2.2" xsi:schemaLocation="hcsc_ectd ../../util/dtd/ca-regional-2-2.xsd"
3       xmlns="hcsc_ectd"   xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
4       xmlns:xlink="http://www.w3.org/1999/xlink">
5       <ectd-regulatory-transaction-information>
16      <m1-administrative-and-product-information>
264  </hcsc_ectd>
```

Figure 1: Example showing XML Declaration

4 EXTENSIBLE MARKUP LANGUAGE (XML) ELEMENTS

4.1 Preparing the electronic Common Technical Document (eCTD) Regulatory Transaction Information

The eCTD Regulatory Transaction Information section allows information about the regulatory activity and regulatory transaction to be included in a form which is easily processed. This information, broadly categorized as metadata, allows Health Canada to more effectively manage incoming electronic regulatory activity and lowers the possibility of errors introduced by manually re-entering this key data.

Most of the elements in this section are required for all regulatory transaction sent to Health Canada. This document provides an overview of expected content from a technical perspective.

Figure 2 shows all possible elements in this section defined by the `<ectd-regulatory-transaction-information>` element, in the required order. This is followed by an element by element description of the expected content. This description includes any schema imposed constraints [that is (i.e.) content rules] for the element. This refers to rules built into the schema itself, which will be enforced by most XML tools. It is important to note that this is separate from the eCTD validation, which the Sponsor should and Health Canada will perform using a dedicated validation tool. This schema validation is considered to be at a lower level and at an earlier point than the eCTD validation.

```
3  <ectd-regulatory-transaction-information>
4    <applicant>My Company</applicant>
5    <product-name>My Product</product-name>
6    <dossier-identifier>e990001</dossier-identifier>
7    <dossier-type>Pharmaceutical Dossier</dossier-type>
8    <regulatory-activity-type>NDS</regulatory-activity-type>
9    <regulatory-activity-lead>Pharmaceutical</regulatory-activity-lead>
10   <sequence-number>0001</sequence-number>
11   <sequence-description>UnDefined Regulatory Transaction</sequence-description>
12   <related-sequence-number>0000</related-sequence-number>
13 </ectd-regulatory-transaction-information>
```

Figure 2: Example showing `<ectd-regulatory-transaction-information>` Element

4.1.1 The <applicant> Element

This mandatory element contains the sponsor's name, i.e. the company which is submitting this regulatory transaction. This element cannot be repeated. There are no schema-level constraints (i.e. content rules) on this element. Great care should be taken to ensure accuracy and consistency with this content. For example, the values “My Company” or “My Company, Inc.” or “My Company, Inc” are all different which may cause difficulties or delays in the processing of the regulatory transaction.

4.1.2 The <product-name> Element

This mandatory element contains the drug name, i.e. the product which is being addressed in this application. This element cannot be repeated. There are no schema-level constraints (i.e. content rules) on this element. Great care should be taken to ensure accuracy and consistency with this content. For example, the values “My Product” or “My product” or “My Product” (note the double space!) are all different which may cause difficulties or delays in the processing of the regulatory transaction.

4.1.3 The <dossier-identifier> Element

This mandatory element contains the unique identifier assigned to this dossier by Health Canada. This element cannot be repeated. It must be in the format “e999999”, i.e. a lower case letter followed by six digits. It is expected that the sponsor will acquire a valid dossier identifier from Health Canada before submitting the initial regulatory transaction.

4.1.4 The <dossier-type> Element

This mandatory element contains the type of dossier, i.e. from a simplistic perspective, whether it is a pharmaceutical or biologic regulatory activity. This element cannot be repeated. The content of this element is taken from a list of values defined by Health Canada and listed in the table below.

Table 1: Dossier Type

Dossier Type	
Biologic Dossier	Includes all regulatory activities under the Biologics and Genetic Therapies Directorate (BGTD) mandate.
Pharmaceutical Dossier	Includes all regulatory activities under the Therapeutic Products Directorate (TPD) mandate.
Drug Master File Dossier	Includes all regulatory activities under the TPD-Bureau of Pharmaceutical Science (BPS), BGTD, Natural Health Products Directorate (NHPD), and Veterinary Drugs Directorate (VDD) mandates as defined in the *Draft Guidance Document – Drug Master Files (DMFs)*

4.1.5 The <regulatory-activity-type> Element

This mandatory element contains the type of the regulatory activity, i.e. from a simplistic perspective, what regulatory purpose this filing is addressing. This element cannot be repeated. The content of this element is taken from a list of values defined by Health Canada and listed in Table 2 below.

Table 2: Regulatory Activity Type

Regulatory Activity Type	
NDS	New Drug Submission
SNDS	Supplement to a New Drug Submission
SNDS-C	Supplement to a New Drug Submission - Conditional
ANDS	Abbreviated New Drug Submission
SANDS	Supplement to an Abbreviated New Drug Submission
NC	Notifiable Change
CTA	Clinical Trial Application
CTA-A	Clinical Trial Application - Amendment
DINA	Drug Identification Number Application
DINB	Drug Identification Number - Biologics
PDC	Post DIN Change
PDC-B	Post DIN Change - Biologics

Regulatory Activity Type	
PSUR-C	Periodic Safety Update Report - Conditional
PSUR-PV	Periodic Safety Update Report - Pharmacovigilance
UD-PV	Undefined Data Pharmacovigilance
RMP-PV	Risk Management Plan - Pharmacovigilance
Level III	Post-Notice of Compliance Changes - Level III
YBPR	Yearly Biologic Product Report
MPNDS	Pre-NDS Meeting
MPSNDS	Pre-SNDS Meeting
MPNC	Pre-NC Meeting
MPDIN	Pre-DIN Meeting
PRECTA	Pre-Clinical Trial Application Meeting
PRNDS	Priority Request NDS
PRSNDS	Priority Request SNDS
PAND	Pandemic Application
DMF Type I	Drug Master File Type I
DMF Type II	Drug Master File Type II
DMF Type III	Drug Master File Type III
DMF Type IV	Drug Master File Type IV
EU NDS	Extraordinary Use New Drug Submission
EU SNDS	Extraordinary Use Supplement to a New Drug Submission
UDRA*	Undefined Regulatory Activity
DSUR	Development Safety Update Report

*Do not use this regulatory activity without prior discussion with Health Canada

4.1.6 The <regulatory-activity-lead> Element

This mandatory element contains which group within Health Canada is expected to take the lead in reviewing the regulatory activity supported by this regulatory transaction. This element cannot be repeated. The content of this element is taken from a list of values defined by Health Canada and listed in the table below.

Table 3: Regulatory Activity Lead

Regulatory Activity Lead	
Pharmaceutical	Includes all regulatory activities under the TPD mandate.
Biological	Includes all regulatory activities under the BGTD mandate.
Post-Market Pharmacovigilance	Includes all regulatory activities under the Marketed Health Products Directorate (MHPD) mandate.

Regulatory Activity Lead	
Drug Master File	Includes all regulatory activities under the TPD - Bureau of Pharmaceutical Sciences (BPS), BGTD, Natural Health Products Directorate (NHPD), and Veterinary Drugs Directorate (VDD) mandates as defined in the *Draft Guidance Document - Drug Master Files (DMFs)*

4.1.7 The <sequence-number> Element

This mandatory element contains a four digit number which is the unique identifier for this sequence (regulatory transaction) inside the overall dossier. This element cannot be repeated. The schema ensures that the content is in the format "9999", i.e. four digits. Internally at Health Canada further validation will be performed to ensure that the number is unique within the dossier, and is greater than previously filed sequence.

The sequence number should have the same value as the corresponding folder name under the main folder, as described in the *Electronic Common Technical Document Specification* (Version 3.2.2).

4.1.8 The <sequence-description> Element

This mandatory element describes the sequence (regulatory transaction) based upon a series of possibilities outlined in Table 4 below. This element cannot be repeated. There are no schema-level constraints (i.e. content rules) on this element. Note that many of the entries below include variable content such as dates, names, protocol numbers, etc.

Table 4: Sequence Description

Sequence Description	Limited to this regulatory activity type only
Administrative	NDS, ANDS, SNDS, SANDS, NC, DINA, DINB, EUNDS, EUSNDS
Cancellation Letter	All types
Change to DIN	DINA, DINB
Comments on Notice of Decision dated mmm. dd, yyyy	NDS
Drug Notification Form	NDS, SNDS, ANDS, SANDS, DINA, DINB, NC, EUNDS, EUSNDS
For Period of mmm. dd, yyyy to mmm. dd, yyyy	PSUR-C, PSUR-PV, YBPR
INITIAL	NDS, ANDS, DINA, DINB, EUNDS,
Minutes of Meeting, mmm. dd, yyyy	All pre-submission meetings
Pandemic Application	Upon consultation
Post-Authorization Division 1 Change	PDC, PDC-B
Post Clearance Data	NDS, SNDS, ANDS, SANDS, NC, EUNDS, EUSNDS, DINA, DINB
Post NOC Change	SNDS, SANDS, EUSNDS, SNDS-C, NC
Year, list of change number (for example: 2012, 15, 19a,….)	Level III Changes
Pre-Submission Meeting Package	NDS, SNDS, NC, DINA, DINB
Priority Review Request	NDS, SNDS
Pristine PM	NDS, SNDS, ANDS, SANDS, SNDS-C, NC, EUNDS, EUSNDS, DINA, DINB
Pristine PM - Second Language	NDS, SNDS, ANDS, SANDS, SNDS-C, NC, EUNDS, EUSNDS, DINA, DINB
Response to BE Clarification Request dated mmm. dd, yyyy	NDS, SNDS, ANDS, SANDS,
Response to Clinical Clarification Request dated mmm. dd, yyyy	NDS, SNDS, ANDS, SANDS, SNDS-C, EUNDS, EUSNDS, NC, DINA, DINB, PSUR-C
Response to e-mail Request dated mmm. dd, yyyy	All types
Response to Labeling Clarification Request dated mmm. dd, yyyy	NDS, SNDS, ANDS, SANDS, SNDS-C, NC, EUNDS, EUSNDS, DINA, DINB
Response to NOC/c-QN dated mmm.dd, yyyy	NDS, SNDS, ANDS, SANDS, SNDS-C, EUNDS, EUSNDS
Response to NOL dated mmm. dd, yyyy	NC
Response to NOD dated mmm. dd, yyyy	NDS, SNDS, ANDS, SANDS, SNDS-C, EUNDS, EUSNDS

Response to NON dated mmm. dd, yyyy	NDS, SNDS, ANDS, SANDS, SNDS-C, EUNDS, EUSNDS
Response to Processing Clarification Request dated mmm. dd, yyyy	All types
Response to Quality and Clinical Clarification Request dated mmm. dd, yyyy	NDS, SNDS, ANDS, SANDS, NC, EUNDS, EUSNDS, DINA, DINB
Response to Quality Clarification Request dated mmm. dd, yyyy	NDS, SNDS, ANDS, SANDS, NC, EUNDS, EUSNDS, DINA, DINB
Response to Screening Acceptance Letter dated mmm. dd, yyyy	NDS, SNDS, ANDS, SANDS, SNDS-C, NC, EUNDS, EUSNDS, DINA, DINB
Response to Screening Clarification Request dated mmm. dd, yyyy	NDS, SNDS, ANDS, SANDS, SNDS-C, NC, EUNDS, EUSNDS, DINA, DINB
Response to SDN dated mmm. dd, yyyy	NDS, SNDS, ANDS, SANDS, SNDS-C, EUNDS, EUSNDS
Response to Telephone Request dated mmm. dd, yyyy	All types
Risk communication document	UD-PV
Post Marketing Surveillance	UD-PV
Benefit Risk Assessment	UD-PV
Signal Work Up	UD-PV
Response to MHPD Requests dated mmm. dd, yyyy	UD-PV
Notification of Change in benefit-risk profile	UD-PV
RMP version <number> dated mmm. dd, yyyy	RMP-PV
Unsolicited Data, <Brief Description>	NDS, SNDS, SANDS, SNDS-C, NC, EUNDS, EUSND, DINA, DINB, UDRA
Comments on Summary Basis of Decision dated mmm. dd, yyyy	NDS, SNDS, EUNDS, EUSNDS, NC
Response to Advisement Letter dated mmm. dd, yyyy	UDRA
DIN Discontinued	UDRA
UFRI Generic Pilot	ANDS, SANDS
Print on Demand	All types

4.1.9 The <related-sequence-number> Element

This optional element contains the four digit sequence number of the first sequence in this regulatory activity. This element cannot be repeated (which is different from Module 1 v1). The schema ensures that the content is in the format “9999”, i.e. four digits.

4.2 Preparing the electronic Common Technical Document (eCTD) Table of Contents (business content)

The <m1-administrative-and-product-information> element contains two broad categories of elements. Heading elements organize all of the electronic documents submitted as part of Module 1 into an electronic Table of Contents. They may be nested to make sub-headings. Leaf elements each describe one document along with other information such as check-sum and eCTD life-cycle information.

There are also special elements called node-extensions which can be used in places where leaf elements are allowed but act like heading elements for grouping documents.

No document (i.e. leaf element) is allowed inside a heading which contains sub-headings. To provide an analogy, leaves can only be at the end of the branches created by the heading elements. This is a change from the CA Module 1 v1.0.

4.2.1 Heading Elements

The top level headings are shown in Figure 3 below, inside the overall surrounding <m1-administrative-and-product-information> element. Note that they are all optional but must be in the order shown.

Please see "Summary of M1 Heading Elements" in Appendix B for a listing of all heading elements and their CTD equivalent terminology.

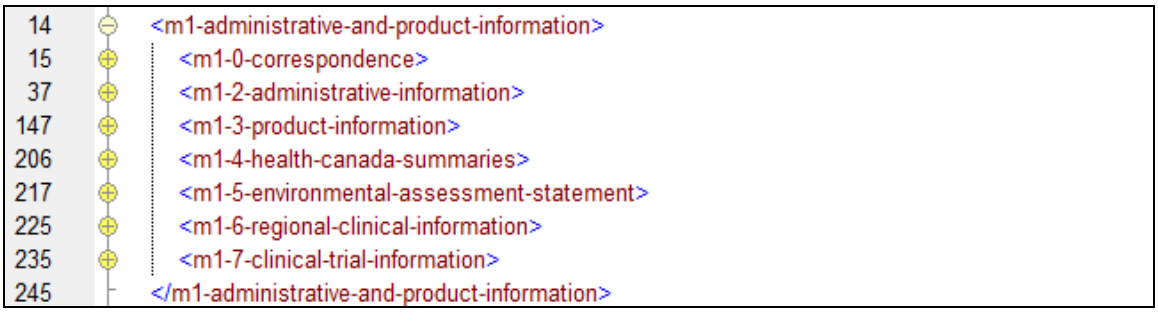

Figure 3: Example showing <m1-administrative-and-product-information>Element

4.2.1.1 The <m1-0-correspondence> Element

This optional element contains various sub-headings related to correspondence. This element cannot be repeated. The schema ensures that the content includes only the allowable sub-headings, as shown in Figure 4. There are no further sub-headings, i.e.

each of the lowest headings below may contain leaf elements. Each of the sub-headings shown is also optional and cannot be repeated.

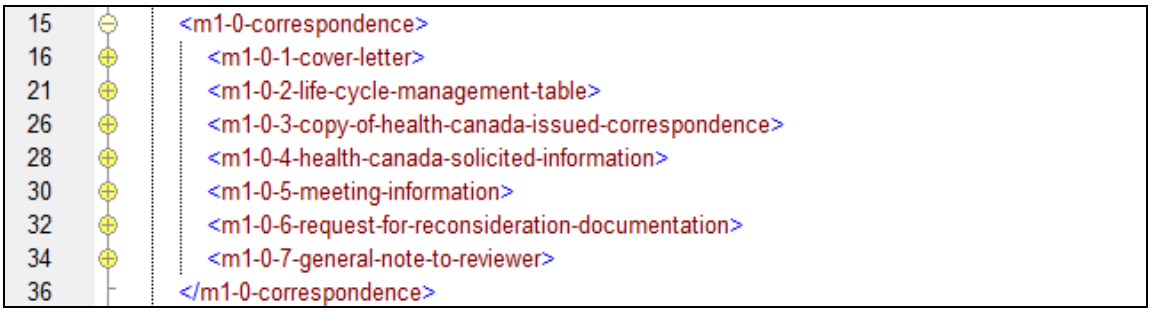

Figure 4: Example showing `<m1-0-correspondence>` Element

4.2.1.2 The <m1-2-administrative-information> Element

This optional element contains various sub-headings related to administrative information. This element cannot be repeated. The schema ensures that the content includes only the allowable sub-headings, as shown in Figure 5. There are no further sub-headings, i.e. each of the lowest headings below may contain leaf elements. Each of the sub-headings shown is also optional and cannot be repeated.

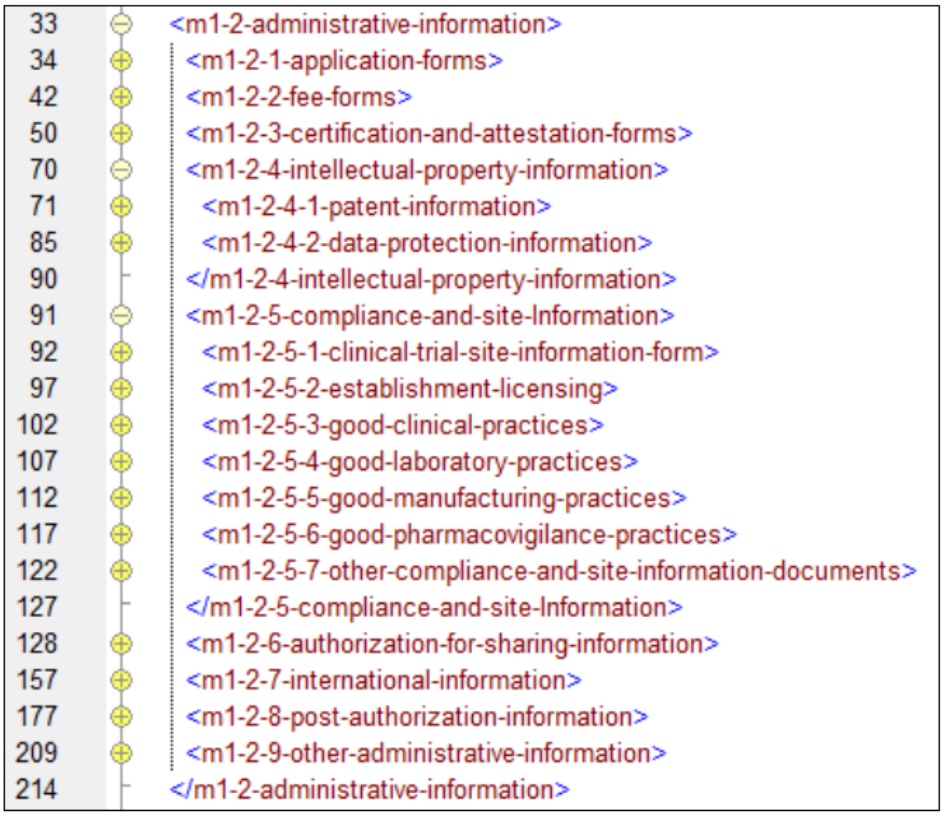

Figure 5: Example showing `<m1-2-administrative-information>` Element

4.2.1.3 The <m1-3-product-information> Element

This optional element contains various sub-headings related to product information. This element cannot be repeated. The schema ensures that the content includes only the allowable sub-headings, as shown in Figure 6. There are no further sub-headings, i.e. each of the lowest headings below may contain leaf elements. Each of the sub-headings shown is also optional and cannot be repeated.

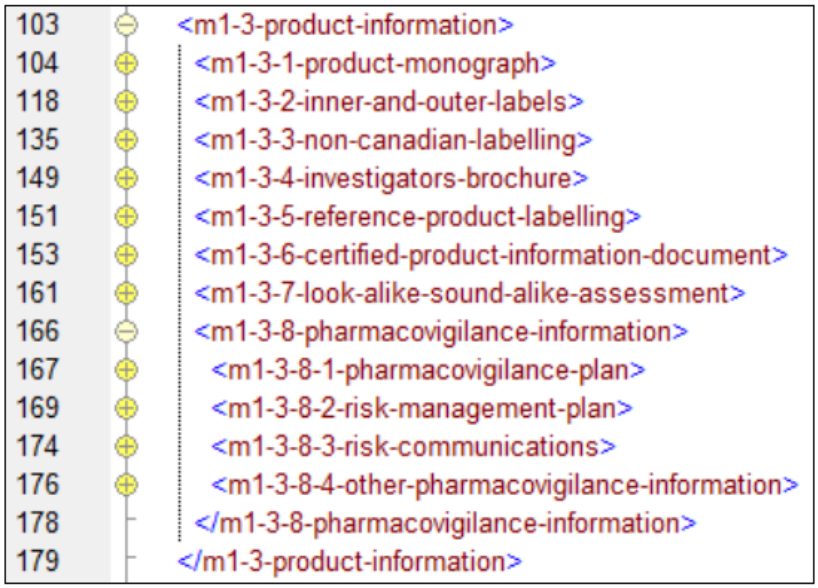

Figure 6: Example showing <m1-3-product-information> Element

4.2.1.4 The <m1-4-health-canada-summaries> Element

This optional element contains various sub-headings related to Health Canada Summaries. This element cannot be repeated. The schema ensures that the content includes only the allowable sub-headings, as shown in Figure 7. There are no further sub-headings, i.e. each of the lowest headings below may contain leaf elements. Each of the sub-headings shown is also optional and cannot be repeated.

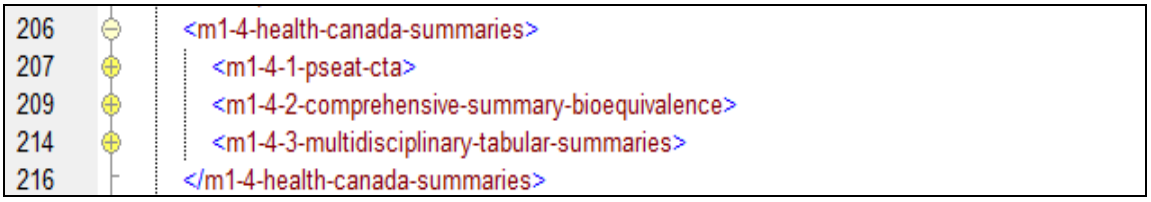

Figure 7: Example showing <m1-4-health-canada-summaries> Element

4.2.1.5 The <m1-5-environmental-assessment-statement> Element

This optional element contains leaf elements (i.e. documents) related to environmental assessment, i.e. there are no sub-headings defined. This element cannot be repeated. The element is shown in Figure 8 with a leaf element.

```
217      <m1-5-environmental-assessment-statement>
218        <leaf ID="Nf6a77b3edadd4f749fda468cfca93760" operation="new" xlink:href="
           0001-ca-m15-env-assess-iv.pdf" checksum="51d79a5ec340f151f2719ba69a33ae30" checksum-type
           ="MD5">
219          <title>0001-ca-m15-env-assess-iv</title>
220        </leaf>
221      </m1-5-environmental-assessment-statement>
```

Figure 8: Example showing `<m1-5-environmental-assessment-statement>` Element

4.2.1.6 The <m1-6-regional-clinical-information> Element

This optional element contains various sub-headings related to regional clinical information. This element cannot be repeated. The schema ensures that the content includes only the allowable sub-headings, as shown in Figure 9. There are no further sub-headings, i.e. each of the lowest headings below may contain leaf elements. Each of the sub-headings shown is also optional and cannot be repeated.

```
225  <m1-6-regional-clinical-information>
226    <m1-6-1-comparative-bioavailability-information>
228    <m1-6-2-company-core-data-sheets>
230    <m1-6-3-priority-review-requests>
232    <m1-6-4-notice-of-compliance-with-conditions>
234  </m1-6-regional-clinical-information>
```

Figure 9: Example showing `<m1-6-regional-clinical-information>` Element

4.2.1.7 The <m1-7-clinical-trial-information> Element

This optional element contains various sub-headings related to clinical trial information. This element cannot be repeated. The schema ensures that the content includes only the allowable sub-headings, as shown in Figure 10. There are no further sub-headings, i.e. each of the lowest headings below may contain leaf elements. Each of the sub-headings shown is also optional and cannot be repeated.

```
235  <m1-7-clinical-trial-information>
236    <m1-7-1-study-protocol>
238    <m1-7-2-informed-consent-forms>
240    <m1-7-3-canadian-research-ethics-board-refusals>
242    <m1-7-4-information-on-prior-related-applications>
244  </m1-7-clinical-trial-information>
```

Figure 10: Example showing `<m1-7-clinical-trial-information>` Element

4.2.2 Leaf Elements

The Canadian Module 1 eCTD backbone file includes document information for each Module 1 document. This information is provided within an XML leaf element as defined by the ICH. Detailed information on leaf elements is provided in the *Electronic Common Technical Document Specification* (Version 3.2.2).

4.2.2.1 The <leaf> Element

This optional element contains one other element, the <title> element along with a number of attributes, all based upon the ICH eCTD definition provided in the *Electronic Common Technical Document Specification* (Version 3.2.2). This element can be repeated. The schema will additionally ensure the checksum-type attribute contains either "MD5" or "md5". An example is provided in Figure 11.

```
28        <leaf ID="ca0001m110100" operation="new" xlink:href="ca110100.pdf" checksum-type="md5"
      checksum="a11d3e5cd24fa823d45e665c4203c18b">
29          <title>Cover letter</title>
30        </leaf>
```

Figure 11: Example showing <leaf> Element

4.2.2.2 The <node-extension> Element

In addition, wherever a <leaf> element is allowed in the schema, a <node-extension> element is also allowed. The <node-extension> structure allows the sponsor to effectively make arbitrary heading structures as desired. This advanced concept can be helpful in organizing multiple large collections of files which are all needing to be placed under a single normal eCTD heading.

The fact that the schema allows the node-extension structure is in compliance with general ICH guidelines, but should not be interpreted as a blanket permission to use the structures anywhere or without consideration. Sponsors may use these structures where needed to assist reviewers but may want to contact Health Canada for advice if the usage is novel.

The optional <node-extension> element contains a single mandatory <title> element, followed by at least one <leaf> element, and followed by another optional <node-extension> element. The element can be repeated.

A purely theoretical example is shown in Figure 12. The concept in the example is a simple Environmental Assessment Statement accompanied by two large Environmental Assessment Reports which have been organized using one and two-tier `<node-extension>` structures.

```
<m1-2-7-international-information>
  <node-extension>
    <title>1.2.7.1 FDA</title>
    <leaf ID="Ne89f9994af7b44ed9d1de3aece1292d6" operation="new" xlink:href="ca145023.pdf" checksum="3ed9f2abe2cff6e526407336d36ea9f9" checksum-type="MD5">
      <title>Foreign refusals</title>
    </leaf>
    <leaf ID="Nf55a9df840384910a50844c53a8c3fde" operation="new" xlink:href="ca145024.pdf" checksum="f99c71d79a787ede7c4fbabb1c9a3520" checksum-type="MD5">
      <title>Foreign review reports</title>
    </leaf>
    <leaf ID="N0d410a1cb5454dad9a45d54c309e48b4" operation="new" xlink:href="ca145025.pdf" checksum="37f77ecb07583ebec276b1594f973dea" checksum-type="MD5">
      <title>Question and Answer (Q and A) documents</title>
    </leaf>
  </node-extension>
  <node-extension>
    <title>1.2.7.2 EMA</title>
    <leaf ID="N2828cc83f0b2493ca32a3b8ffdff2a60" operation="new" xlink:href="ca145026.pdf" checksum="3ed9f2abe2cff6e526407336d36ea9f9" checksum-type="MD5">
      <title>Foreign refusals</title>
    </leaf>
    <leaf ID="N489b9001fdb041858ee47c92dc6de2f7" operation="new" xlink:href="ca145027.pdf" checksum="5c8c1f022fb19755afe04c4370bce592" checksum-type="MD5">
      <title>Foreign review reports</title>
    </leaf>
    <leaf ID="Naece5d42ec784d24aaf84f431d057f6f" operation="new" xlink:href="ca145028.pdf" checksum="5c8c1f022fb19755afe04c4370bce592" checksum-type="MD5">
      <title>Question and Answer (Q and A) documents</title>
    </leaf>
  </node-extension>
</m1-2-7-international-information>
```

Figure 12: Example showing `<node-extension>` Elements

5 ELECTRONIC COMMON TECHNICAL DOCUMENT (ECTD) PREPARATION TOOLS

Health Canada does not mandate or recommend any particular software product for eCTD preparation. However, based upon observing and assisting many sponsors with thousands of electronic regulatory activities Health Canada recommends that:

- Prepare the eCTD using an authenticated commercial eCTD Preparation software.

  There are a wide variety of options available to sponsors for commercial eCTD preparation software, both in terms of multiple vendors and in terms of approaches [for example (e.g.) installed software, software as a service, service providers]. Sponsors are encouraged to find a solution which supports current and ongoing Health Canada eCTD requirements and meets their overall business needs.

- Validate the prepared regulatory activity using an authenticated commercial eCTD Validation tool.

Sponsors are encouraged to use a validation tool which supports checking current and ongoing Health Canada eCTD requirements. These validation tools are not just XML "checkers" or "parsers", but actually evaluate the technical content of the regulatory activity. There are numerous options available to sponsors, several of which are free. This minimizes the possibility of technical validation errors with eCTD regulatory transactions sent to Health Canada which introduce delays into the overall regulatory process.

APPENDICES

APPENDIX A: REFERENCES

Health Canada References:

The latest versions of these and other Health Canada guidance documents, policies, templates and forms can be obtained from the Health Canada website at:

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/index-eng.php
http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/index-eng.php

- *Guidance for Industry: Preparation of Drug Regulatory Activities in the eCTD Format*
- HC SC 3011: Drug Application for: Human, Veterinary, or Disinfectant Drugs and Clinical Trial Applications/Attestation
- *Guidance for Industry: Management of Drug Submissions*

International Conference on Harmonisation (ICH) References

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

- *Electronic Common Technical Document Specification (Version 3.2.2)*
- *eCTD IWG Question and Answer and Specification Change Request Document*

APPENDIX B: SUMMARY OF MODULE 1 HEADING ELEMENTS

The following table summarizes the heading elements found in the Canadian Module 1 Schema Version 2.2. Certain elements (e.g. "1.1 Table of Contents") have not been included in the eCTD as they are required only for paper regulatory activities, not for electronic regulatory activities in eCTD format.

Table 5: Summary of M1 Heading Elements

Section ID	Business Terminology	Related XML Element	Occurrence Coding
1	Administrative and Product Information	m1-administrative-and-product-information	1 .. 1
1.0	Correspondence	m1-0-correspondence	0 .. 1
1.0.1	Cover letter	m1-0-1-cover-letter	0 .. 1
1.0.2	Life Cycle Management Table	m1-0-2-life-cycle-management-table	0 .. 1
1.0.3	Copy of Health Canada issued correspondence	m1-0-3-copy-of-health-canada-issued-correspondence	0 .. 1
1.0.4	Health Canada Solicited Information	m1-0-4-health-canada-solicited-information	0 .. 1
1.0.5	Meeting Information	m1-0-5-meeting-information	0 .. 1
1.0.6	Request for Reconsideration Documentation	m1-0-6-request-for-reconsideration-documentation	0 .. 1
1.0.7	General Note to Reviewer	m1-0-7-general-note-to-reviewer	0 .. 1
1.2	Administrative Information	m1-2-administrative-information	0 .. 1
1.2.1	Application Forms	m1-2-1-application-forms	0 .. 1
1.2.2	Fee Forms	m1-2-2-fee-forms	0 .. 1
1.2.3	Certification and Attestation Forms	m1-2-3-certification-and-attestation-forms	0 .. 1
1.2.4	Intellectual Property Information	m1-2-4-intellectual-property-information	0 .. 1
1.2.4.1	Patent Information	m1-2-4-1-patent-information	0 .. 1
1.2.4.2	Data Protection Information	m1-2-4-2-data-protection-information	0 .. 1
1.2.5	Compliance and Site Information	m1-2-5-compliance-and-site-Information	0 .. 1
1.2.5.1	Clinical Trial Site Information Form	m1-2-5-1-clinical-trial-site-information-form	0 .. 1
1.2.5.2	Establishment Licensing	m1-2-5-2-establishment-licensing	0 .. 1
1.2.5.3	Good Clinical Practices	m1-2-5-3-good-clinical-practices	0 .. 1
1.2.5.4	Good Laboratory Practices	m1-2-5-4-good-laboratory-practices	0 .. 1
1.2.5.5	Good Manufacturing Practices	m1-2-5-5-good-manufacturing-practices	0 .. 1

1.2.5.6	Good Pharmacovigilance Practices	m1-2-5-6-good-pharmacovigilance-practices	0 .. 1
1.2.5.7	Other Compliance and Site Information	m1-2-5-7-other-compliance-and-site-information	0 .. 1
1.2.6	Authorization for Sharing Information	m1-2-6-authorization-for-sharing-information	0 .. 1
1.2.7	International Information	m1-2-7-international-information	0 .. 1
1.2.8	Post- Authorization Information	m1-2-8-post-authorization-information	0 .. 1
1.2.9	Other Administrative Information	m1-2-9-other-administrative-information	0 .. 1
1.3	Product Information	m1-3-product-information	0 .. 1
1.3.1	Product Monograph	m1-3-1-product-monograph	0 .. 1
1.3.2	Inner and Outer Labels	m1-3-2-inner-and-outer-labels	0 .. 1
1.3.3	Non-Canadian Labelling	m1-3-3-non-canadian-labelling	0 .. 1
1.3.4	Investigator's Brochure	m1-3-4-investigators-brochure	0 .. 1
1.3.5	Reference Product Labelling	m1-3-5-reference-product-labelling	0 .. 1
1.3.6	Certified Product Information Document	m1-3-6-certified-product-information-document	0 .. 1
1.3.7	Look-alike/Sound-alike Assessment	m1-3-7-look-alike-sound-alike-assessment	0 .. 1
1.3.8	Pharmacovigilance Information	m1-3-8-pharmacovigilance-information	0 .. 1
1.3.8.1	Pharmacovigilance Plan	m1-3-8-1-pharmacovigilance-plan	0 .. 1
1.3.8.2	Risk Management Plan	m1-3-8-2-risk-management-plan	0 .. 1
1.3.8.3	Risk Communications	m1-3-8-3-risk-communications	0 .. 1
1.3.8.4	Other Pharmacovigilance Information	m1-3-8-4-other-pharmacovigilance-information	0 .. 1
1.4	Health Canada Summaries	m1-4-health-canada-summaries	0 .. 1
1.4.1	PSEAT-CTA	m1-4-1-pseat-cta	0 .. 1
1.4.2	Comprehensive Summary : Bioequivalence	m1-4-2-comprehensive-summary-bioequivalence	0 .. 1
1.4.3	Multidisciplinary Tabular Summaries	m1-4-3-multidisciplinary-tabular-summaries	0 .. 1
1.5	Environmental Assessment Statement	m1-5-environmental-assessment-statement	0 .. 1
1.6	Regional Clinical Information	m1-6-regional-clinical-information	0 .. 1
1.6.1	Comparative Bioavailability Information	m1-6-1-comparative-bioavailability-information	0 .. 1
1.6.2	Company Core Data Sheets	m1-6-2-company-core-data-sheets	0 .. 1
1.6.3	Priority Review Requests	m1-6-3-priority-review-requests	0 .. 1

1.6.4	Notice of Compliance with Conditions	m1-6-4-notice-of-compliance-with-conditions	0 .. 1
1.7	Clinical Trial Information	m1-7-clinical-trial-information	0 .. 1
1.7.1	Study Protocol	m1-7-2-study-protocol	0 .. 1
1.7.2	Informed Consent Forms	m1-7-3-informed-consent-forms	0 .. 1
1.7.3	Canadian Research Ethics Board (REB) Refusals	m1-7-4-canadian-research-ethics-board-refusals	0 .. 1
1.7.4	Information on Prior-related Applications	m1-7-5-information-on-prior-related-applications	0 .. 1

APPENDIX C: DEFINITIONS

Dossier - A collection of all regulatory activities throughout the life cycle of a product (e.g. human drug, veterinary drug, medical device, food).

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, etc.

Regulatory Transaction - An information package sent by the sponsor 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 etc.).

Undefined Regulatory Activity (UDRA) - A regulatory activity that has not been requested by Health Canada (unsolicited information) or other regulatory activities not listed in Table 2.

Undefined Data Pharmacovigilance (UDPV) - Post-market pharmacovigilance data such as: Risk communication document, Post Marketing Surveillance, Benefit Risk Assessment, Signal Work Up, Response to MHPD Requests for Additional Information, and Notification of Change in benefit-risk profile.

Response to Processing Clarification Request - A response to a request made during the processing stage by the Office of Submissions and Intellectual Property (OSIP).

APPENDIX D: SCHEMA FILES

Primary file: ca-regional-2-2.xsd

```
<?xml version="1.0" encoding="UTF-8"?>
<xs:schema xmlns:xs="http://www.w3.org/2001/XMLSchema" xmlns="hcsc_ectd"
xmlns:xlink="http://www.w3.org/1999/xlink" targetNamespace="hcsc_ectd" elementFormDefault="qualified"
attributeFormDefault="unqualified">
	<xs:import namespace="http://www.w3.org/1999/xlink" schemaLocation="xlink.xsd"/>
	<xs:import namespace="http://www.w3.org/XML/1998/namespace" schemaLocation="xml.xsd"/>
<!--
################################
 Health Canada root definition
################################
-->
	<xs:element name="hcsc_ectd">
		<xs:complexType>
			<xs:sequence>
				<xs:element ref="ectd-regulatory-transaction-information"/>
				<xs:element ref="m1-administrative-and-product-information"/>
			</xs:sequence>
			<xs:attribute name="schema-version" use="required">
				<xs:simpleType>
					<xs:restriction base="xs:decimal">
						<xs:enumeration value="2.2"/>
					</xs:restriction>
				</xs:simpleType>
			</xs:attribute>
		</xs:complexType>
	</xs:element>
	<!--
################################
Health Canada specific data types
################################
-->
	<!--
================================
Probable values to change begin here
================================
-->
	<xs:simpleType name="ca-dossier-type">
		<xs:restriction base="xs:string">
			<xs:enumeration value="Biologic Dossier"/>
			<xs:enumeration value="Pharmaceutical Dossier"/>
			<xs:enumeration value="Drug Master File Dossier"/>
		</xs:restriction>
	</xs:simpleType>
	<xs:simpleType name="ca-regulatory-activity-type">
		<xs:restriction base="xs:string">
```

```
                        <xs:enumeration value="NDS"/>
                        <xs:enumeration value="SNDS"/>
                        <xs:enumeration value="SNDS-C"/>
                        <xs:enumeration value="ANDS"/>
                        <xs:enumeration value="SANDS"/>
                        <xs:enumeration value="NC"/>
                        <xs:enumeration value="CTA"/>
                        <xs:enumeration value="CTA-A"/>
                        <xs:enumeration value="DINA"/>
                        <xs:enumeration value="DINB"/>
                        <xs:enumeration value="PDC"/>
                        <xs:enumeration value="PDC-B"/>
                        <xs:enumeration value="PSUR-C"/>
                        <xs:enumeration value="PSUR-PV"/>
                        <xs:enumeration value="UD-PV"/>
                        <xs:enumeration value="RMP-PV"/>
                        <xs:enumeration value="Level III"/>
                        <xs:enumeration value="YBPR"/>
                        <xs:enumeration value="MPNDS"/>
                        <xs:enumeration value="MPSNDS"/>
                        <xs:enumeration value="MPNC"/>
                        <xs:enumeration value="MPDIN"/>
                        <xs:enumeration value="PRECTA"/>
                        <xs:enumeration value="PRNDS"/>
                        <xs:enumeration value="PRSNDS"/>
                        <xs:enumeration value="PAND"/>
                        <xs:enumeration value="DMF type I"/>
                        <xs:enumeration value="DMF type II"/>
                        <xs:enumeration value="DMF type III"/>
                        <xs:enumeration value="DMF type IV"/>
                        <xs:enumeration value="EU NDS"/>
                        <xs:enumeration value="EU SNDS"/>
                        <xs:enumeration value="UDRA"/>
                        <xs:enumeration value="DSUR" />
                </xs:restriction>
        </xs:simpleType>
        <xs:simpleType name="ca-regulatory-activity-lead">
                <xs:restriction base="xs:string">
                        <xs:enumeration value="Pharmaceutical"/>
                        <xs:enumeration value="Biological"/>
                        <xs:enumeration value="Post-Market Pharmacovigilance"/>
                        <xs:enumeration value="Drug Master File"/>
                </xs:restriction>
        </xs:simpleType>
        <!--
================================
Probable values to change end here
================================
-->
        <xs:simpleType name="ca-dossier-id">
```

```
                <xs:restriction base="xs:string">
                        <xs:pattern value="[a-z][0-9]{6}"/>
                </xs:restriction>
        </xs:simpleType>
        <xs:simpleType name="ca-sequence-no">
                <xs:restriction base="xs:integer">
                        <xs:pattern value="[0-9]{4}"/>
                </xs:restriction>
        </xs:simpleType>
        <xs:complexType name="ca-leaf-ext">
                <xs:sequence minOccurs="0" maxOccurs="unbounded">
                        <xs:choice>
                                <xs:element ref="leaf"/>
                                <xs:element ref="node-extension"/>
                        </xs:choice>
                </xs:sequence>
        </xs:complexType>
        <!--
################################
ICH specific schema data types
################################
-->
        <xs:simpleType name="ich-checksum-type">
                <xs:restriction base="xs:string">
                        <xs:enumeration value="MD5"/>
                        <xs:enumeration value="md5"/>
                </xs:restriction>
        </xs:simpleType>
        <xs:simpleType name="ich-leaf-operations">
                <xs:restriction base="xs:string">
                        <xs:enumeration value="new"/>
                        <xs:enumeration value="append"/>
                        <xs:enumeration value="replace"/>
                        <xs:enumeration value="delete"/>
                </xs:restriction>
        </xs:simpleType>
        <!--
================================
Leaf content per ICH
================================
-->
        <xs:element name="leaf">
                <xs:complexType>
                        <xs:sequence>
                                <xs:element ref="title"/>
                                <xs:element ref="link-text" minOccurs="0"/>
                        </xs:sequence>
                        <xs:attribute name="ID" type="xs:ID" use="required"/>
                        <xs:attribute name="operation" type="ich-leaf-operations" use="required"/>
                        <xs:attribute ref="xlink:href"/>
```

```
                <xs:attribute name="modified-file" type="xs:string"/>
                <xs:attribute name="checksum-type" type="ich-checksum-type"/>
                <xs:attribute name="checksum" type="xs:string"/>
                <xs:attribute name="application-version" type="xs:string"/>
                <xs:attribute name="version" type="xs:string"/>
                <xs:attribute name="keywords" type="xs:string"/>
                <xs:attribute name="font-library" type="xs:string"/>
                <xs:attribute ref="xlink:type"/>
                <xs:attribute ref="xlink:role"/>
                <xs:attribute ref="xlink:show"/>
                <xs:attribute ref="xlink:actuate"/>
                <xs:attribute ref="xml:lang"/>
        </xs:complexType>
</xs:element>
<xs:element name="node-extension">
        <xs:complexType>
                <xs:sequence>
                        <xs:element ref="title"/>
                        <xs:element ref="leaf" maxOccurs="unbounded"/>
                        <xs:element ref="node-extension" minOccurs="0"/>
                </xs:sequence>
                <xs:attribute name="ID" type="xs:ID"/>
                <xs:attribute ref="xml:lang"/>
        </xs:complexType>
</xs:element>
<xs:element name="title">
        <xs:complexType>
                <xs:simpleContent>
                        <xs:extension base="xs:string">
                                <xs:attribute name="ID" type="xs:ID"/>
                        </xs:extension>
                </xs:simpleContent>
        </xs:complexType>
</xs:element>
<xs:element name="link-text">
        <xs:complexType>
                <xs:sequence>
                        <xs:element ref="xref" minOccurs="0"/>
                </xs:sequence>
                <xs:attribute name="ID" type="xs:ID"/>
        </xs:complexType>
</xs:element>
<xs:element name="xref">
        <xs:complexType>
                <xs:attribute name="ID" type="xs:ID" use="required"/>
                <xs:attribute ref="xlink:type"/>
                <xs:attribute ref="xlink:role"/>
                <xs:attribute ref="xlink:title"/>
                <xs:attribute ref="xlink:href"/>
                <xs:attribute ref="xlink:show"/>
```

```
                </xs:complexType>
        </xs:element>
        <!--
################################
Health Canada introductory content (meta data) structure
################################
-->
        <xs:element name="ectd-regulatory-transaction-information">
                <xs:complexType>
                        <xs:sequence>
                                <xs:element ref="applicant"/>
                                <xs:element ref="product-name"/>
                                <xs:element ref="dossier-identifier"/>
                                <xs:element ref="dossier-type"/>
                                <xs:element ref="regulatory-activity-type"/>
                                <xs:element ref="regulatory-activity-lead"/>
                                <xs:element ref="sequence-number"/>
                                <xs:element ref="sequence-description"/>
                                <xs:element ref="related-sequence-number" minOccurs="0"/>
                        </xs:sequence>
                </xs:complexType>
        </xs:element>
        <xs:element name="applicant" type="xs:string"/>
        <xs:element name="product-name" type="xs:string"/>
        <xs:element name="dossier-identifier" type="ca-dossier-id"/>
        <xs:element name="dossier-type" type="ca-dossier-type"/>
        <xs:element name="regulatory-activity-type" type="ca-regulatory-activity-type"/>
        <xs:element name="regulatory-activity-lead" type="ca-regulatory-activity-lead"/>
        <xs:element name="sequence-number" type="ca-sequence-no"/>
        <xs:element name="sequence-description" type="xs:string"/>
        <xs:element name="related-sequence-number" type="ca-sequence-no"/>
        <!--
################################
Health Canada business content structure
################################
-->
        <xs:element name="m1-administrative-and-product-information">
                <xs:complexType>
                        <xs:sequence>
                                <xs:element ref="m1-0-correspondence" minOccurs="0"/>
                                <xs:element ref="m1-2-administrative-information" minOccurs="0"/>
                                <xs:element ref="m1-3-product-information" minOccurs="0"/>
                                <xs:element ref="m1-4-health-canada-summaries" minOccurs="0"/>
                                <xs:element ref="m1-5-environmental-assessment-statement" minOccurs="0"/>
                                <xs:element ref="m1-6-regional-clinical-information" minOccurs="0"/>
                                <xs:element ref="m1-7-clinical-trial-information" minOccurs="0"/>
                        </xs:sequence>
                </xs:complexType>
        </xs:element>
        <xs:element name="m1-0-correspondence">
```

```
                <xs:complexType>
                        <xs:sequence>
                                <xs:element ref="m1-0-1-cover-letter" minOccurs="0"/>
                                <xs:element ref="m1-0-2-life-cycle-management-table" minOccurs="0"/>
                                <xs:element ref="m1-0-3-copy-of-health-canada-issued-correspondence"
minOccurs="0"/>
                                <xs:element ref="m1-0-4-health-canada-solicited-information"
minOccurs="0"/>
                                <xs:element ref="m1-0-5-meeting-information" minOccurs="0"/>
                                <xs:element ref="m1-0-6-request-for-reconsideration-documentation"
minOccurs="0"/>
                                <xs:element ref="m1-0-7-general-note-to-reviewer" minOccurs="0"/>
                        </xs:sequence>
                </xs:complexType>
        </xs:element>
        <xs:element name="m1-0-1-cover-letter" type="ca-leaf-ext"/>
        <xs:element name="m1-0-2-life-cycle-management-table" type="ca-leaf-ext"/>
        <xs:element name="m1-0-3-copy-of-health-canada-issued-correspondence" type="ca-leaf-ext"/>
        <xs:element name="m1-0-4-health-canada-solicited-information" type="ca-leaf-ext"/>
        <xs:element name="m1-0-5-meeting-information" type="ca-leaf-ext"/>
        <xs:element name="m1-0-6-request-for-reconsideration-documentation" type="ca-leaf-ext"/>
        <xs:element name="m1-0-7-general-note-to-reviewer" type="ca-leaf-ext"/>
        <xs:element name="m1-2-administrative-information">
                <xs:complexType>
                        <xs:sequence>
                                <xs:element ref="m1-2-1-application-forms" minOccurs="0"/>
                                <xs:element ref="m1-2-2-fee-forms" minOccurs="0"/>
                                <xs:element ref="m1-2-3-certification-and-attestation-forms" minOccurs="0"/>
                                <xs:element ref="m1-2-4-intellectual-property-information" minOccurs="0"/>
                                <xs:element ref="m1-2-5-compliance-and-site-Information" minOccurs="0"/>
                                <xs:element ref="m1-2-6-authorization-for-sharing-information"
minOccurs="0"/>
                                <xs:element ref="m1-2-7-international-information" minOccurs="0"/>
                                <xs:element ref="m1-2-8-post-authorization-information" minOccurs="0"/>
                                <xs:element ref="m1-2-9-other-administrative-information" minOccurs="0"/>
                        </xs:sequence>
                </xs:complexType>
        </xs:element>
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