Health Canada Santé Canada

Guidance Document

Guidance document: Preparation of regulatory activities in non-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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Document change log

Date	Description
May 08, 2024	Revision required to update the Appendix F: Electronic Submission Gateway, remove of the Appendix E: UDRA Table and revisions to improve clarity throughout the document.
June 09, 2023	Revision required to update the Appendix G Electronic Submission Gateway, mandatory use of web-based Master File Application form and minor revision to improve clarity throughout the document.
October 1, 2022	Revisions required for mandatory use of Regulatory Enrolment Process (REP) for veterinary drugs, transmission and top level folder requirements for Developmental Safety Update Reports (DSUR), cover letter changes for Master files, directorate name change to Pharmaceutical Drugs Directorate (PDD), new Electronic Submission Gateway (ESG) Accounts Management Portal and minor revision to improve clarity throughout the document.
February 28, 2022	Medical Device information has been removed, information for regulatory activities that are mandatory in eCTD format has been removed, and updated information has been provided for revised processes and requirements
October 31, 2016	Updates to Medical device and Veterinary Drugs
February 29, 2016	Div.1, Div.5, Div.8, DSUR, Post-market Vigilance, Level III, DNF and MF
September 25, 2015	Guidance Document: Preparation of Drug Regulatory Activities in non-eCTD Format
June 15, 2015	Notice: Health Canada's requirements for filing a regulatory activity in "non-eCTD electronic-only" format

Foreword

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document must be supported by adequate justification. They 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 always, Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us adequately assess the safety, efficacy or quality of a therapeutic product. We are committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read along with the relevant sections of the regulations and other applicable guidance documents.

Table of Contents

1. Introduction

This document defines the filing requirements and provides guidance on the structure, content and transmission of regulatory transactions filed in the non-electronic common technical document (non-eCTD) format.

Health Canada has published requirements for the mandatory filing of specified regulatory activities in eCTD format. Refer to the Filing Submissions Electronically information page for more comprehensive requirements on filing in electronic common technical document (eCTD) format.

1.1 Policy objectives

The objective of this document is to provide operational direction and guidance to sponsors and Health Canada staff on the requirements for the preparation of:

- Regulatory activities for Human drugs and disinfectants pursuant to Part C - Division 1 and Division 5 of the *Food and Drug Regulations*
- Regulatory activities for Veterinary drugs pursuant to Part C - Division 1 and Division 8 of the *Food and Drug Regulations*
- Master Files (MFs)

1.2 Policy statements

Health Canada has established the following options that are available for filing regulatory activities in scope of this document and their related subsequent transactions:

Drugs and disinfectants for human use (Division 1)

- Health Canada accepts regulatory activities for Division 1 human drugs in non-eCTD format.
- Use of the Regulatory Enrolment Process (REP) is mandatory. Refer to the REP information page for detailed information.
- Regulatory activities for Division 1 human drugs can also be filed in eCTD format. Refer to the Filing Submissions Electronically information page for detailed information related to the eCTD format.

Drugs for clinical trials involving human subjects (Division 5)

- Health Canada accepts clinical trial regulatory activities in the non-eCTD format.
- Use of the REP is not available for clinical trial regulatory transactions.
- Regulatory activities for clinical trials can also be filed in eCTD format. Refer to the Filing Submissions Electronically information page for detailed information related to the eCTD format.

Positron-emitting radiopharmaceuticals (PERs) used in basic clinical research studies (Division 3)

- Health Canada accepts Basic Research Applications: Positron-emitting radiopharmaceuticals (BRAP) regulatory activities filed in the non-eCTD format.

- Use of the REP is not available for BRAP regulatory transactions.

Veterinary drugs

- Health Canada accepts veterinary drug regulatory activities filed in the non-eCTD format.
- Use of the REP is mandatory (with exception to Experimental Studies Certificate (ESC), Investigational New Drug (IND) and their amendments). Refer to the REP information page for detailed information.

Medical devices

- Health Canada accepts regulatory activities for medical devices in the non-eCTD format. However, instructions are no longer provided in this guidance document. Refer to the page of Guidance Documents for Medical Devices for detailed information.
- Use of REP is available for regulatory activities for medical devices. Refer to the REP information page for detailed information.

Master files

- Health Canada accepts regulatory transactions for existing master files in non-eCTD format, where the master file number has already been assigned.
- Use of the web-based Master File Application form is mandatory.
- All new master files must be filed in eCTD format**.** Refer to the Filing Submissions Electronically information page for detailed information related to the eCTD format.

1.3 Glossary of terms

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.

Control number (Submission Number): A six (6) digit unique number assigned by Health Canada for each regulatory activity submitted by a stakeholder.

Dossier: A collection of all regulatory activities throughout the life cycle of a product or products (with the same medicinal ingredient(s)) for a stakeholder.
Note: For clinical trials, it is a collection of all regulatory activities throughout the life cycle of a single clinical trial protocol.

Dossier Identifier (ID): A code assigned by Health Canada to uniquely identify the dossier. The dossier ID is also referred to as the Top Level Folder Name. It consists of a lowercase letter followed by six (6) or seven (7) unique numbers depending on the regulatory activity type.

Drug Identification Number (DIN): An eight (8) digit numerical code assigned to each drug product in final dosage form approved under the *Food and Drugs Act* and its Regulations.

Drug Product (Dosage Forms): The finished product (e.g., tablets, capsules, injections, etc.).

Drug Substance (Drug Substances or Intermediates in the Production of Drug Substances): A pharmacologically active ingredient.

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

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

Protocol Number: A protocol number is a variable length, alpha-numeric sequence used by stakeholders to assign a reference number to their protocol. The protocol number for clinical trials should remain the same for the duration of the trial.

Regulatory Activity: A collection of all regulatory transactions throughout the process of a specific activity.

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, response to Notice of Non-Compliance (NON), Response to Notice of Deficiency (NOD) or Drug Notification Form (DNF)).

Solicited and unsolicited information: Solicited information is considered any information that is requested by Health Canada during the processing, screening or review of a submission/application.

- Solicited Information such as responses to Screening Deficiency Notice (SDN), NOD, NON or Response to a Clarification Request (e.g. response to telephone request, response to email request, response to screening Acceptance Letter, etc.).
- Unsolicited information such as safety information, company name change during review or product name change during review.

Note: For more details about solicited and unsolicited information, see Guidance Document: Management of Drug Submissions and Application.

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

Common Electronic Submission Gateway (CESG): CESG is an Agency-wide solution for providing electronic regulatory transactions. The CESG enables the secure submission of premarket and post-market regulatory information for review.
The CESG is the central transmission point for sending information electronically to the Health Canada. Within that context, the CESG is a conduit along which submissions travel to reach the proper Health Canada Directorate, Bureau, or Office.

Drug Submission Tracking System – Industry Access (DSTS-IA):
This system is web-based portal that enables individual users to access information such as submission numbers, dossier ID, submission status, etc. about specific drug submissions, limited by the specific company or companies whose information they have been given permission to

access. Users require accounts to access the information. An account can be requested by emailing the Client Information Unit at client.information@hc-sc.gc.ca.

1.4 Background

The non-eCTD guidance document was initially published in 2015 and has been revised several times to reflect the onboarding of additional product lines to the non-eCTD format. This revision prescribes changes that have resulted since the previous version, stemming from various process implementations, such as the mandatory use of the eCTD format and the REP.

Consequently, the scope of non-eCTD format has decreased as mandatory eCTD format became more predominant. Furthermore, the REP was implemented for certain product lines to further align the intake process by facilitating the transmission of non-eCTD transactions via CESG, which would otherwise be sent on media.

1.5 Scope and application

The regulatory activities listed below and related regulatory transactions are **in scope** for filing in non-eCTD format.

Human drugs and disinfectants

Division 1

- Application for Drug Identification Number (DINA)
- Application for Drug Identification Number - Biologic (DIN-B)
- Application for Drug Identification Number - Disinfectant (DIN-D)
- Application for Drug Identification Number - Category IV Product (DIN-F)
- Post-Authorization Division 1 Change (PDC)
- Post-Authorization Division 1 Change - Biologic (PDC-B)
- Post-DIN Notification
- Notices of Change: Level III (for DINB only)
- Yearly Biologic Product Report (YBPR) – Biologic products
- Pre-Submission Meeting Information (MPDIN)
- Undefined Regulatory Activity (UDRA)
- Periodic Safety Update Report (PSUR-PV) or Periodic Benefit Risk Evaluation Report (PBRER-PV) when provided to the Marketed Health Products Directorate (MHPD)
- Risk Management Plan (RMP-PV), when provided to MHPD
- Post-market Vigilance data 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 5

- Clinical Trial Application (CTA)

- Clinical Trial Application - Amendment (CTA-A)
- Clinical Trial Application - Notification (CTA-N)
- Pre-Clinical Trial Application Consultation Meeting (Pre-CTA)

Division 3

- Basic Research Applications: positron-emitting radiopharmaceuticals (BRAP)

Master files (existing master files only)

- Type I - Active substance master file
- Type II - Container Closure System and Component master file
- Type III - Excipient master file
- Type IV - Dosage form master file
- Type V - Facilities and equipment master file

Veterinary drugs

- New Drug Submission (NDS), including regulatory activities for administrative changes
- Abbreviated New Drug Submission (ANDS), including regulatory activities for administrative changes
- Supplement to a New Drug Submission (SNDS), including regulatory activities for administrative changes
- Supplement to an Abbreviated New Drug Submission (SANDS), including regulatory activities for administrative changes
- Notifiable Change (NC), including regulatory activities for administrative changes
- Periodic Safety Update Report Post-market Vigilance (PSUR-PV)
- Application for Drug Identification Number Application - Veterinary (DINV)
- Experimental Studies Certificate (ESC)
- Experimental Studies Certificate (ESC) Amendments
- Investigational New Drug (IND)
- Investigational New Drug (IND) Amendments
- Protocol Review (PRORE)
- Post-Notice of Compliance Changes: Level III Form
- Submissions for international collaborative reviews, such as those under the Regulatory Cooperation Council (RCC)
- Pre-Submission Meeting Information (e.g.: MPNDS, MPSNDS, MPDINV, MPSANDS, MPANDS, or MPESC)

Other

- Developmental Safety Update Report (DSUR)

The regulatory information listed below are **out of scope** for filing in non-eCTD format.

- 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)
- 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 stakeholder
- New Certificate of Supplementary Protection (CSP) Applications
- CSP related Correspondence
- Court documents (e.g. statements of claim, notices of application, notices of motion, etc.)
- Pipeline meeting

2. Structure and content

All regulatory activities and subsequent regulatory transactions that are filed for review to Health Canada **must** be provided using the appropriate folder structure and document placement. Failure to file a transaction using the correct folder structure may result in the transaction not being accepted by Health Canada.

- General requirements for folder structure are provided in this guidance document.
- Zipped folder structures, for specific product lines, are available on the Filing Submissions Electronically information page. Stakeholders can use them to build a regulatory transaction for filing to Health Canada.
- Details on the correct module 1 sub folders to place the documents in the regulatory transaction for human drugs and disinfectants, can be found on the Organization and Document Placement for Canadian Module 1 document available on the Filing Submissions Electronically information page.

2.1 Cover letter

The cover letter provides a brief description of what is in a regulatory transaction, which is used to support the processing of the transaction. Every regulatory transaction must be filed with an electronic cover letter, with the exception of transactions that contain only a Post NOC - Level III Changes Form. The information entered on the Regulatory Enrolment Process Regulatory Transaction template must align with the information on the cover letter. Delays will occur if conflicting information is provided, as Health Canada will need to confirm the intent to accurately process the transaction.

Below are some of the general requirements for cover letters:

- Regulatory transactions that are sent on media should include a paper cover letter in addition to the electronic copy.
- A cover letter must be less than four (<4) pages in length.
- A cover letter does not require a signature.
- A cover letter must only contain the required subset of information, as prescribed below; no supporting data should be included.

Health Canada requires the following content for all cover letters:

- Clearly state what is being provided
- Reason for filing
- Stakeholder Name and Role (e.g. Sponsor, Manufacturer, DIN Owner, or Agent)
- Brand name
- Dossier Identifier (ID) – if using REP and for all Master Files
- Regulatory Activity type
- Control number (if known)
- 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)
- 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
- Indicate the contact name and email address where the Validation Report (if required) should be sent
- Responses to requests for clarification should clearly indicate the name of the requester

In addition to the above general requirements, the cover letters for the following transactions should include detailed information:

- Other Sale Notifications:
    - Notification for Interruption of Sale (DIN Dormant) 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)
    - Discontinuation of Sale Notification should indicate the:
        - DIN(s) to be cancelled
        - Discontinuation date
        - Expiry date of the last lot sold
        - Lot number of the last lot sold
- 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)
    - 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)
- DSUR should also indicate which of the following applies:
    - REQUESTED - as per a request made by Health Canada
    - VOLUNTARY - important new safety information
- Clinical Trial regulatory transactions should include the relevant protocol number
- Master file conversions and reactivations must indicate if there is a new Letter of Access included, that has not been previously authorized
- Withdrawal of Letters of Access, Agent withdrawal and Agent name change for Master Files should clearly indicate the name of the company and agent name
- DINA regulatory activities should indicate if there is a labelling reference product

The cover letter must not contain the following:

- Scientific information
- Summary response in a Question and Answer format
- Response to request for additional information
- List of documents provided in the transaction

2.2 Folder structure and file naming convention

The content of the regulatory transaction filed for review must be organized in folders. Multiple documents must not be bundled into one file, but instead provided as separated documents. Each file/document must be placed in the required subfolders aligning with the appropriate structure. The complete folder structure for the following product lines is available as zipped file on the Filing Submissions Electronically information page. These zipped files can be downloaded and used to prepare a regulatory transaction for filing:

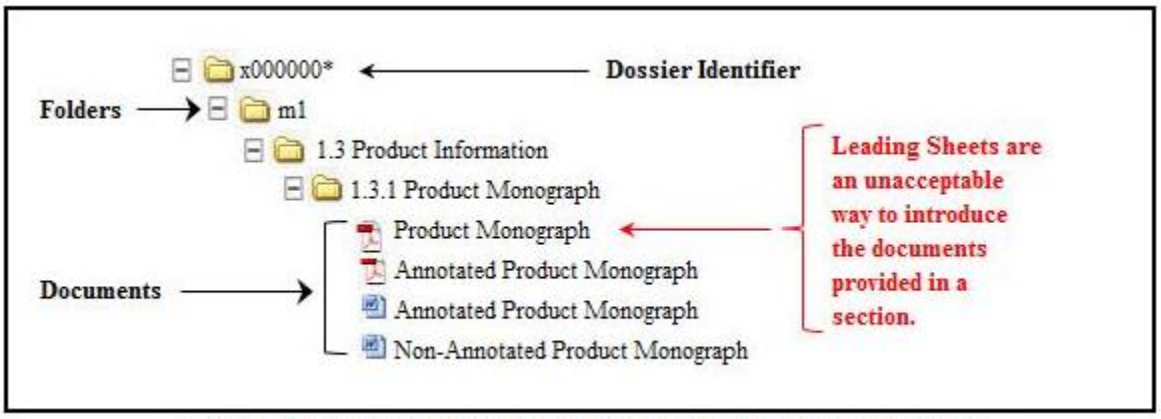
- Division 1 human drugs and disinfectants
- Division 5 human drugs
- Master Files
- Veterinary drugs (Division 1 and 8)

The following are common folders structure errors to avoid:

- The top level folder **must** be the dossier ID for regulatory transactions using the REP or MF XML file; otherwise the transaction will fail validation.
- The top level folder **must not** contain any files; it should only contain the required sub-folders.
- Multiple documents provided, as a single PDF file is **not acceptable.**
- Information provided in previous transactions must **not** be provided again, unless it is affected by a change (such as a MF update, MF letter of access, administrative change, and response to SDN).
- Empty folders **must not** be included in the structure (i.e. If you are using the zipped folder structures, ensure that all subfolders that do not contain a file are deleted prior to sending the transaction to Health Canada).

- Leading sheets at the beginning of sub-folders (indicating a folder is **not** applicable or describing the content) **must not** be provided.

Figure 1: Leading sheet



* A letter followed by 6 or 7 digits depending on the regulatory activity type.

For a detailed list of what files/documents to include in each folder, refer to the Organisation and Document Placement for Canadian Module 1 available on the Filing Submissions Electronically information page. For information on Modules 2-5 of the CTD structure, refer to the ICH M4: The Common Technical Document (CTD) developed by the International Council for Harmonisation (ICH).

For a detailed list of what files/documents to include in each folder for Veterinary Drugs transactions refer to Appendix V: Master Index of Guidance for Industry Preparation of Veterinary New Drug submissions and Appendix E of this document.

2.2.1 Top level folder/dossier identifier

The top level folder is the main folder of a regulatory transaction that is filed to Health Canada and must be included with every transaction. All the subfolders and content files are located within the top level folder.

The top level folder must be the dossier identifier (dossier ID), unless specified otherwise below. The dossier ID is a **lower case letter:**

- followed by six digits for pharmaceutical, biological, clinical trial, veterinary dossiers
- followed by seven digits for master file dossiers

All regulatory activities and associated transactions for a dossier must be filed under the same dossier ID. For product line specific details, see sections below and Table 1: Dossier information for summary.

Human drugs and disinfectants

If the dossier ID is unknown, it must be requested using the appropriate dossier ID request form **prior** to filing.

For an existing dossier, we recommend that you first use the Drug Submission Tracking System – Industry Access (DSTS-IA) to look up the assigned dossier ID. This can be done by searching for a recent regulatory activity submitted to Health Canada that has the same medicinal ingredient(s) and brand name as the one you intend to file. If you do not have access to DSTS-IA, please contact the Office of Submission and Intellectual Property at client.information@hc-sc.gc.ca for information on creating a DSTS-IA account.

Note: For regulatory transactions being filed under the administrative pathway, a new dossier ID may be required. Please refer to the instructions on the "Help Text" section of the Dossier ID Request Form for details.

Veterinary drugs

If the dossier ID is unknown, it must be requested using the appropriate dossier ID request form **prior** to filing.

For an existing dossier, we recommend that you first use the Drug Submission Tracking System – Industry Access (DSTS-IA) to look up the assigned dossier ID. This can be done by searching for a recent regulatory activity submitted to Health Canada that has the same medicinal ingredient(s) and/or brand name as the one you intend to file. If you do not have access to DSTS-IA, please contact the Office of Submission and Intellectual Property at client.information@hc-sc.gc.ca for information on creating a DSTS-IA account.

Note: For regulatory transactions being filed under the administrative pathway, a new dossier ID may be required. Please refer to the instructions on the "Help Text" section of the Dossier ID Request Form for details.

The dossier ID request does not apply to: Experimental Studies Certificate (ESC), Investigational New Drug (IND) and their amendments.

Clinical trials

For the first transaction associated with a new protocol, the top level folder must be the product name or the protocol number. The dossier ID will be issued upon receipt of the pre-submission meeting or clinical trial application and must be used for all subsequent transactions associated with this protocol.

For the first transaction associated with a new DSUR, the top level folder must be the product name. The dossier ID will be issued upon receipt of the DSUR and must be used for all subsequent DSURs or DSUR related transactions.

The dossier ID request does not apply to Clinical trials.

Master files

If you do not know your master file number, please contact the Master file unit at dmf.enquiries-fmm@hc-sc.gc.ca.

The dossier ID request does not apply to Master files.

Table 1: Dossier information

Dossier type	Dossier ID format	Dossier ID request
Pharmaceutical	dXXXXXX*	Dossier ID request form
Biological	dXXXXXX*	Dossier ID request form
Veterinary	vXXXXXX*	Dossier ID request form with exception to ESC, IND and their amendments
Clinical trial	cXXXXXX*	Dossier ID request does not apply
Master file	fXXXXXXX**	Dossier ID request does not apply

*followed by six digits for pharmaceutical, biological, clinical trial, veterinary dossiers
**followed by seven digits for master file dossiers

Where applicable, a request for a dossier ID should be sent a maximum of eight weeks prior to filing a regulatory transaction. Dossier IDs that have not been used within **12 months** 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.

2.2.2 Common Technical Document (CTD) folder structure

The ICH CTD structure must be used to organize the documents provided for human drug and disinfectant regulatory transactions, pursuant to division 1, division 5 or master files. This structure consists of five (5) modules, each containing multiple subfolders to be used for specific documents.

Module 1 folders

The requirements for module 1 of the CTD structure is regional and therefore defined by Health Canada. Refer to the Organisation and Document Placement for Canadian Module I, available on the Filing Submissions Electronically page for a detailed list of the documents required in each subfolder in this module.

Specific module 1 requirements by product line:

Clinical trials

- When filing clinical trial applications, stakeholders may also refer to "Table 1: Contents of Submission Package in accordance with CTD Format" of the Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications for further clarity.

Master files

- When providing MF Types I, II, III, IV & V the folders in module 1 will be considered as the Restricted Part (RP). See Appendix C of this document for illustrations.
- Refer to the Guidance Document: Master Files (MFs) – Procedures and Administrative Requirements as well as the folder structures provided in the Appendix C of this document for more information on the structure of module 1 for each MF transaction type.

Veterinary drugs

- Refer to section 2.2.3 of this guidance document for veterinary drug folder structure.

Modules 2 to 5 folders

The structure and names of the modules 2 to 5 folders are defined in the M4: Common Technical Document found on the International Council for Harmonisation (ICH) website. When providing information in the module 3: Regional Information section, the following subfolders should be created for specific documents:

- 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
- 3.2.R.5 Assessment of Similarity
- 3.2.R.6 On Site Evaluation
- 3.2.R.7 Other Regional Information
- 3.2.R.8 Product Lifecycle Management Information

Specific modules 2 to 5 requirements by product line:

Clinical trials

- When filing clinical trial applications, stakeholders may also refer to "Table 1: Contents of Submission Package in accordance with CTD Format" of the Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications for further clarity.
- When providing literature references related to non-clinical or clinical studies, they should be placed in module 4 (section 4.3 Literature References, non-clinical related) or module 5 (section 5.4 Literature References, clinical related). If providing study related information, such as study synopses, study summary, they should also be placed in appropriate sections and subsections of module 4 and module 5 respectively.

Master files

- When providing MF Types I & IV, two separate documents should be included in the folder "2.3 Quality Overall Summary," a "QOS (RP)" and a "QOS (AP)" file.

- When providing an MF Type I – Drug Substance (for illustration see figure C-1):
  - The folder "3.2.S Drug Substance" should be duplicated and each clearly identified as either the Applicant's Part or the Restricted Part using the abbreviations "AP" or "RP" respectively.
  - The folder "3.2.A Appendices" will be considered as the Restricted Part (RP).

- When providing an MF Type II – Container Closure Systems (for illustration see figure C-2), there are two possible options for structuring the folders in Module 3:
  - A separate subfolder under "3.2.P.7 Container Closer System" can be used for each component provided, or
  - The folder "3.2.P Drug Products" (with all its subfolders) can be used for information that is common to all components and separate subfolders under "3.2.P.7 Container Closer System" can be used for information specific to each component.

- When providing an MF Type III – Excipients (for illustration see figure C-3):
  - The folder "3.2.P.4 Control of Excipients" in module 3 should be duplicated for each excipient provided.

- When providing an MF Type IV – Drug Products (for illustration see figure C-4):
  - The folder "3.2.P Drug Products" should be duplicated and each clearly identified as either the Applicant's Part or the Restricted Part using the abbreviations "AP" or "RP" respectively.
  - The folders "3.2.A Appendices" and "3.2.R Regional Information" will be considered as the Restricted Part (RP).

2.2.3 Veterinary drugs folder structure

The structure and name of the folders for veterinary drug regulatory activities are defined in Appendix V: "Master Index" of Health Canada's Guidance for Industry: Preparation of Veterinary New Drug Submissions and the Appendix E of this document.

A zipped folder structure is also available on the Filing Submissions Electronically page to assist stakeholders in preparing their regulatory activities.

Post – NOC Level III changes forms should be structured as outlined in Appendix E – Figure E-4 of this document.

2.3 File naming convention

With the exception of the file extension, the file naming convention within each folder is left to the stakeholder preparing the regulatory transaction. However, Health Canada suggests that the file names be kept as brief and meaningful as possible, while adhering to the following:

- File names should describe the content in a meaningful way and must be limited to a maximum of 50 characters, including the file extension.
- Commonly used and meaningful abbreviations, such as QOS for Quality Overall Summary, may be used to shorten file names.
- Files provided electronically must not be password protected.
- REP file names are system generated and **must** not be modified.

3. Technical requirements for regulatory activities

3.1 File format

Electronic documents should be provided in pdf format (portable document format, versions 1.7, PDF/A-1 and PDF/A-2) unless otherwise specified in table 2. PDF documents with attachments are not allowed.

The documents in the Table 2 must be provided in PDF and/or Word 365 format(s) as specified. PDF documents should be generated from electronic source documents and not from scanned materials, except where access to an electronic source document is unavailable or where a signature is required.
It is important that PDF files be properly bookmarked. Rule of thumb for good bookmarking include:

- Documents that are ten pages or more should be bookmarked.
- Bookmarks are used by Health Canada as a document Table of Contents and should not include the regulatory activity level.
- Sections, subsections, tables, figures, and appendices should all be bookmarked.
- Having too many levels of bookmarks is 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.

It is important that PDF files be properly hyperlinked:

- Hyperlinks within the same PDF document are acceptable, but hyperlinks between different documents are **not** to be used.
- It is the responsibility of the stakeholder preparing the regulatory transaction to ensure that hyperlinks are functioning.
- Links must also include references to the specific section or page in the event the link is broken.

- The required hyperlinks to related information should be included only in the PDF version of files.

Table 2: Specific file format requirements for drugs

List of Documents provided with Human Drugs		**File Format***	
		PDF	**Word**
Certified Product Information Document (CPID)	Annotated	√	-
	Non-annotated	-	√
Comprehensive Summary: Bioequivalence		√	√
HC-SC3011 Form (if not using REP)		√	-
Label Safety Assessment Update - Sponsor Attestation		√	√
Product Monograph (PM)/Prescribing Information	Annotated	√	√
	Non-annotated	-	√
	Second language	√	-
Protocol Safety and Efficacy Assessment Template (PSEAT) - CTA		-	√
Quality Overall Summary (QOS)	Clinical Trial Applications	-	√
	All other regulatory activities in scope of non-eCTD format	√	√
Response document for responses to clarification requests, SDN, NON, NOD		√	√
('√' = Required / '-' = Not Applicable)			
* When PDF **and** Word are selected, the document should be provided in both formats * HC-SC3011 can be provided in PDF **or** Word format. Both formats are not required.			

- Presentations for meetings with Health Canada (e.g., pre-submission meetings), can be provided in PowerPoint 365 (.pptx) format.
- Division 1 – 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".
- Regulatory Enrolment Process (REP) files must be provided in XML format. For more information, refer to the REP information page.
- Master file application form must be provided in XML format.

To obtain a complete list of acceptable file formats, size of files, etc. refer to the non-eCTD validation rules available on the Filing Submissions Electronically information page.

Contact us for other file formats that may be acceptable. See Appendix B for contact information.

3.2 Signatures

Documents that legally require signatures may be signed with an electronic signature (e.g. an image of the official's wet ink signature, digital signature), or the signature page can be printed, signed, scanned and saved as a pdf file.

If only one page of a multi-page PDF document contains a signature, the stakeholder 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).

The cover letter does not require a signature. However, contact information, including printed name, phone number, and email address, should be provided.

3.3 Validation of transaction

All regulatory transactions should be validated prior to transmitting to Health Canada. For validation criteria refer to the posted validation rules on Health Canada's website.

3.4 Transmission of electronic data

The acceptable method of transmissions are CESG, media and email. All other methods of transmission, such as Dropbox and secure FTP sites, are not acceptable.

3.4.1 Sent via the CESG

The use of the CESG is mandatory to the following regulatory transactions:

- Transactions within scope of REP [Drugs and disinfectants for human use (Division 1), Veterinary drugs]
- Transactions for master files [with web-based MF Application form]

Prior to using the CESG for sending transactions, stakeholders must register as a trading partner. For detailed information on how to become a trading partner, refer to the CESG information page, and Appendix F of this Guidance document.

3.4.2 Sent on media

Regulatory transactions not accepted via CESG, should be provided on media. A paper copy of the cover letter and media should be mailed to the appropriate address as indicated in Appendix B of this document.
The accepted media formats for providing electronic regulatory transactions are:

- Compact Disc-Recordable (CD-R) conforming to the Joliet specification
- Universal Serial Bus (USB) 2.0 or 3.0 drive
- Digital Versatile Disc (DVD-RAM and DVD+R/-R) in Universal Disk Format (UDF) standard

All media should be labelled. The label on the disc/drive should contain the following information:

- Stakeholder Name
- Brand Name
- Dossier ID (if known)

Subsequent to burning the CD/DVD or transferring data to a drive, stakeholders should ensure that **all** files can be opened, files are not corrupted, and that "Thumb.db" files are removed.

Clinical trial and DSUR
Clinical Trial regulatory transactions and DSURs must be sent directly to the appropriate Directorate (Office of Clinical Trials at PDD for Pharmaceuticals or Office of Regulatory Affairs at BRDD for Biologics and radiopharmaceuticals) to the address outlined in Appendix B of this document.

3.4.3 Sent via email

The below specified regulatory transactions may/should be provided to Health Canada via email. However, the stakeholder assumes the risk of transmitting "Protected B" information through email.

Regulatory transactions provided by email should meet the following requirements:

- The maximum email size accepted by the corporate mail server is 20 megabytes, anything larger should be sent on media.
- If the regulatory transaction is provided via email, a duplicate copy must not be provided by mail.
- The regulatory transaction should be organized in folders (see section 2.2 of this guidance document) and provided as a zipped file.
- The body of the email should only contain the zipped regulatory transaction; no other documents or related information should be included.
- Zipped files and documents contained in the email should not be password protected.

Clinical trials
If the clinical trial related transaction is larger than 20 megabytes, the transaction may be split and sent as separate emails (e.g. one email for Module 1, and one email for Module 2/3). The

subject line of the emails should clearly link to one another (e.g. "Email 1 of 2" and relevant subject line).

- Responses to a Clarification Request (IR) for Clinical Trials **should** be sent via email:
    - Email should be addressed to the requestor(s) identified in the clarification request.
    - The subject line of the email should include the statement:
        - "Division 5 - IR (< Protocol Number(s)>, <Control Number(s)>)"
    - The zipped file should be named:
        - "IR (<Protocol Number(s)>, <Control Number(s)>)".
- Responses to a No Objection Letter (NOL) for Clinical Trials **can** be sent via email to:
    - brdd.cta-dec.dmbr@hc-sc.gc.ca for biologic and radiopharmaceutical drugs.
    - The subject line of the email should include the statement:
        - "Division 5 – Response to CTA/CTA-A NOL (<Protocol Number(s)>, <Control Number(s)>)"
    - The zipped file should be named:
        - "Response to CTA/CTA-A NOL (<Protocol Number(s)>, <Control Number(s)>)"
- Clinical Trial Application Notifications (CTA-N) should be sent via email to:
    - brdd.ctan-ndec.dmbr@hc-sc.gc.ca for biologic and radiopharmaceutical drugs
    - oct.ctan-ndec.bec@hc-sc.gc.ca for pharmaceutical drugs
    - The subject line of the email should include the statement:
        - "Division 5 – CTA-N (, <Protocol Number(s)>, <Parent CTA Control Number(s)>)".
    - The zipped file should be named:
        - "CTA-N (<Protocol Number(s)>, <Parent CTA Control Number(s)>)".
- DSURs should be sent via email to:
    - brdd.cta-dec.dmbr@hc-sc.gc.ca for biologic and radiopharmaceutical drugs
    - pdd-pv-dmp@hc-sc.gc.ca for pharmaceutical drugs
    - The subject line of the email should include the statement: "DSUR – drug name".
    - The zipped file should be named: "DSUR-drugname".
- Basic Research Application: PERS (BRAP) regulatory transaction should be sent via email to brdd.bra-daerf.dmbr@hc-sc.gc.ca.

3.5 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.

At each technical evaluation stage, a written correspondence from Health Canada will be issued via email if there are errors or deficiencies identified with the transaction. Stakeholders 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.

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

During the technical evaluation process, the document content of the regulatory transaction is not reviewed. When the technical evaluation of the regulatory transaction has been completed, the administrative, screening, and/or evaluation process is initiated.

The technical evaluation process has three stages:

3.5.1 CESG compliance

For transactions received via the CESG, 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 Appendix F of this Guidance document.

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

3.5.2 Technical validation

The technical validation is conducted by a validation software using the latest published validation rules for the non-eCTD format.

If technical validation fails, a Validation Report describing the errors will be emailed, as a PDF attachment, to the stakeholder.

3.5.3 Manual verification

The third stage is a manual verification of the particular regulatory transaction type as per the submission/application processing section and associated timelines as outlined in the Guidance Document: The Management of Drug Submissions and Applications, or the Guidance Document: Master Files (MFs) – Procedures and Administrative Requirements. In addition, verification of the placement of documents, particularly in Module 1 is conducted.

4. Important considerations

1. For transactions sent incorrectly via the CESG, the stakeholder must notify Health Canada via email prior to modifying and/or resending the transaction via CESG. Health Canada will provide instructions on how to proceed. Do not resend without prior consultation and confirmation.
2. Issues found during the technical evaluation such as CESG compliance issues, technical validation errors, or manual processing issues (e.g. incorrect structure) will result in Health Canada sending a validation report and/or processing hold email. To resolve such errors and issues, stakeholders are required to correct the failed transaction and re-file

the whole transaction.
However, if Health Canada is requesting missing documents, new documents, or corrections 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 a subsequent transaction with the requested documents only. In these cases, do not re-submit the entire original submission in your subsequent transaction, addressing the deficiency is sufficient. Include a new cover letter in module 1.0.1 explaining the reason for filing. In addition include a copy of the issued correspondence in module 1.0.3 – Health Canada issued correspondence, REP regulatory transaction or MF xml file (when sending via the CESG) and new or revised requested documents. The information on how to refile a transaction which failed validation or has missing or incorrect documents are always outlined in the Health Canada issued correspondence.

3. The content of the regulatory activity in non-eCTD format is the legal document; therefore, convenience copies provided directly to reviewers via email (with the exception of those indicated in section 3.4.3 of this document) have no legal value and will not be uploaded on the Health Canada internal systems.
4. When providing MF Types I, II, III, IV & V, the folders in Module 1 will be considered as the Restricted Part (RP). See Appendix E of this document for illustrations.
5. Stakeholders should contact the applicable review bureau to confirm prior to filing if they are unsure of which regulatory activity type to file.
6. Regulatory transactions using REP:
    - If a stakeholder is filing transactions using the REP, requirements for 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.
7. Switching from non-eCTD to eCTD format:
   For human drugs and disinfectants, switching from non-eCTD to eCTD format is permitted with a new regulatory activity (i.e. sequence 0000 should be the first transaction for a new regulatory activity) or once a regulatory activity has been cleared (i.e. sequence 0000 can be post-clearance data). Switching format in the middle of screening/review is not permitted (i.e. sequence 0000 cannot be a response to clarification request transaction).

   For information regarding conversions of Master Files from non-eCTD to eCTD format, refer to the Master File Guidance Document.

Appendices

Appendix A: Other resources

This resource should be read in conjunction with the following resources however not limited to:

- Documents available on the Filing Submissions Electronically page
- Documents available on the REP information page
- Guideline on Preparation of Drug Identification Number Submissions
- Guidance Document on Post-Drug Identification Number (DIN) Changes
- Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications
- Guidance Document: The Management of Drug Submissions and Applications
- Guidance Document: Post-Notice of Compliance (NOC) Changes: Quality Document
- Guidance Document: Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document
- Guidance Document: Post-Notice of Compliance (NOC) Changes: Framework Document
- Guidance Document: Administrative Processing of Submissions and Applications Involving Human or Disinfectant Drugs
- Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements
- Guidance for Industry Preparation of Veterinary New Drug Submissions
- Guidance for Industry - Management of Regulatory Submissions (for Veterinary Drugs)
- Guidance for Industry - Preparation of Veterinary Abbreviated New Drug Submissions - Generic Drugs
- Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format

Appendix B: Contacts

General enquiries electronic submissions: ereview@hc-sc.gc.ca

Master file enquiries: dmf.enquiries-fmm@hc-sc.gc.ca

Clinical trial applications – Pharmaceuticals
Office of Clinical Trials
Pharmaceutical Drugs Directorate
Health Canada
5th Floor, Holland Cross, Tower B
1600 Scott Street, Address Locator 3105A
Ottawa, ON, Canada
K1A 0K9

General enquiries email: oct.enquiries-requetes.bec@hc-sc.gc.ca
CTA-N email: oct.ctan-ndec.bec@hc-sc.gc.ca
DSUR email: pdd-pv-dmp@hc-sc.gc.ca

Clinical trial applications - Biologics and radiopharmaceuticals

Office of Regulatory Affairs
Biologics and Radiopharmaceutical Drugs Directorate
Ground Floor, Health Canada Building #6
100 Eglantine Driveway
Address Locator 0601C
Ottawa, ON, Canada
K1A 0K9

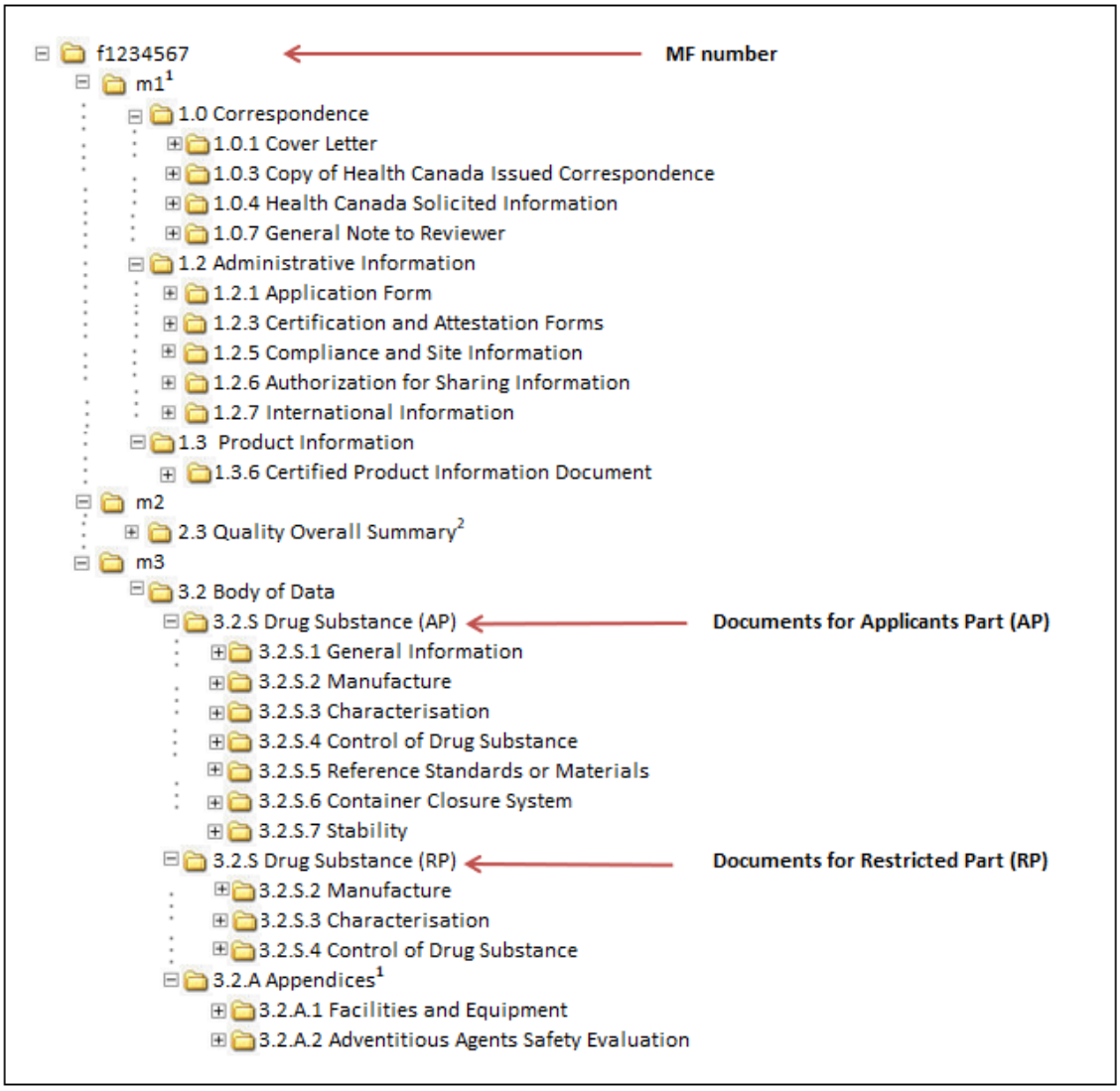
General Enquiries email: brdd.ora@hc-sc.gc.ca
CTA-N email: brdd.ctan-ndec.dmbr@hc-sc.gc.ca

Veterinary Drugs Directorate (VDD)
General enquiries email: vdd.skmd.so-dgps.dmv.cp@hc-sc.gc.ca

Other
Contact information for specific review center/bureau/office responsibilities can be found in the Guidance Document: Management of Drug Submissions and Applications

Appendix C: Master files sample folder structure(s)

Figure C-1: MF Type I - Drug Substance



1. All documents in this folder will be considered Restricted Part (RP) of the MF.
2. Two separate documents (both in pdf and word format) should be submitted in the folder "2.3 Quality Overall Summary," a "QOS (RP)" and a "QOS (AP)" file.
3. (AP) or (RP) should be used in the subfolder names to identify if the folder is Applicants Part or Restricted Part.

Figure C-2: MF Type II – Container Closure Systems and Components

Two options are recommended for providing multiple components in the M3 folder.

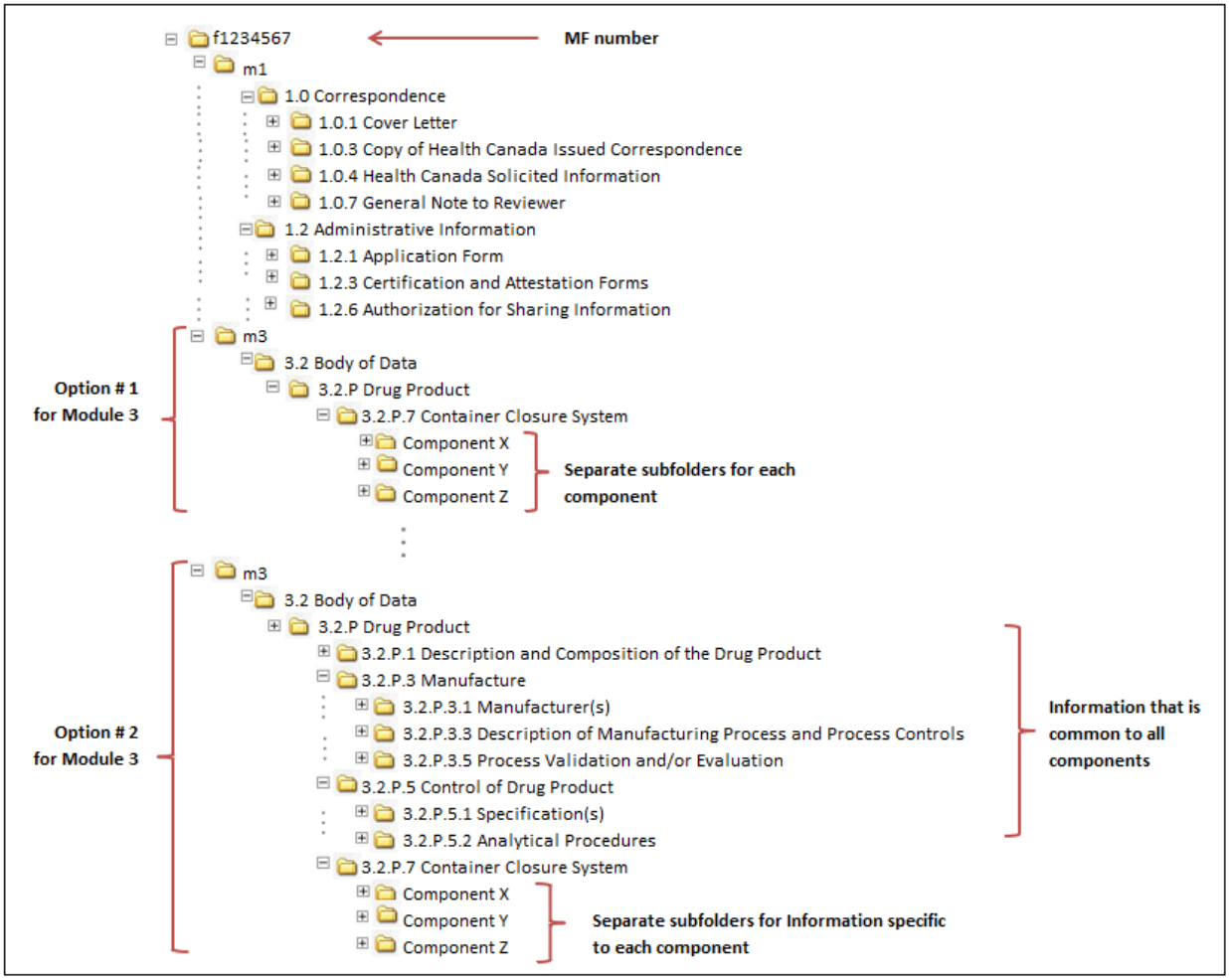


Figure C-3: MF Type III – Excipients

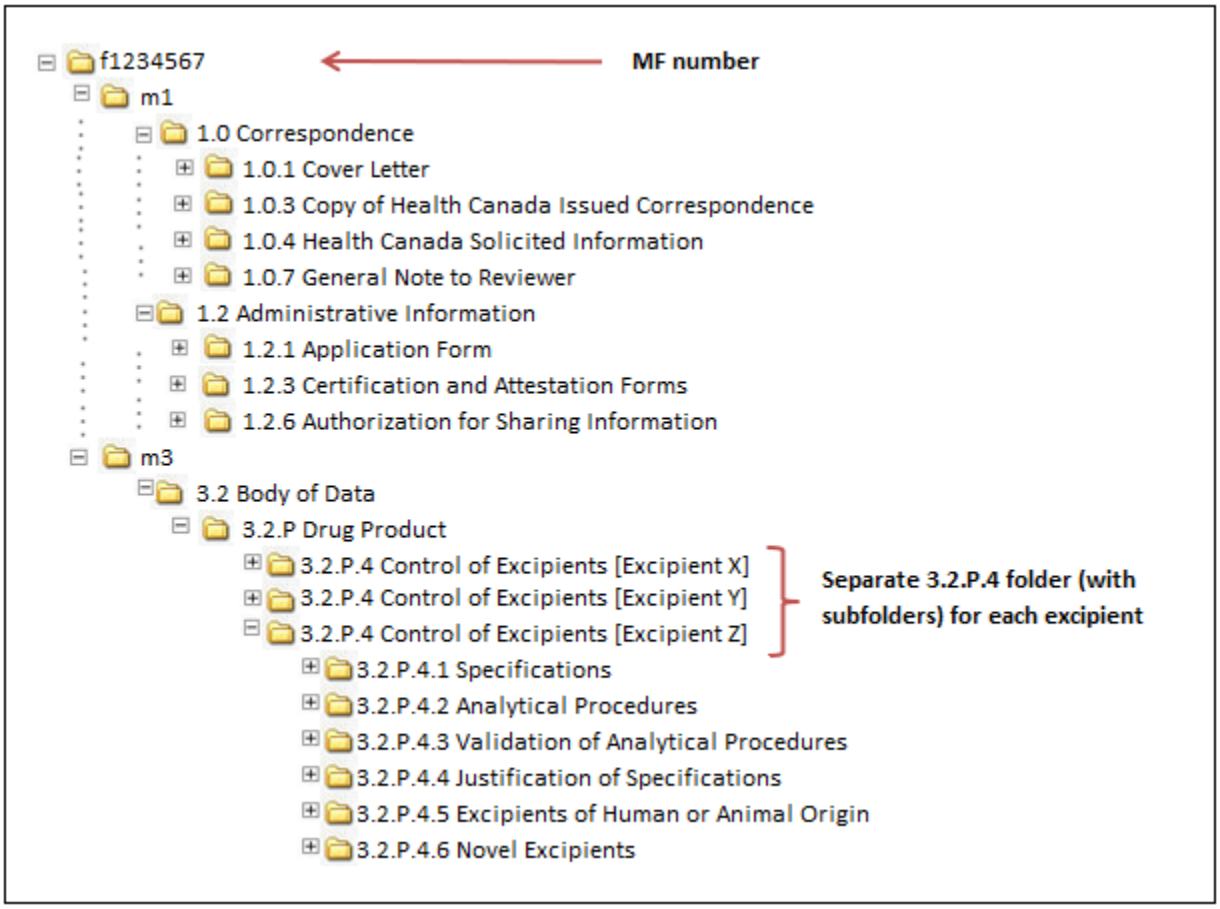
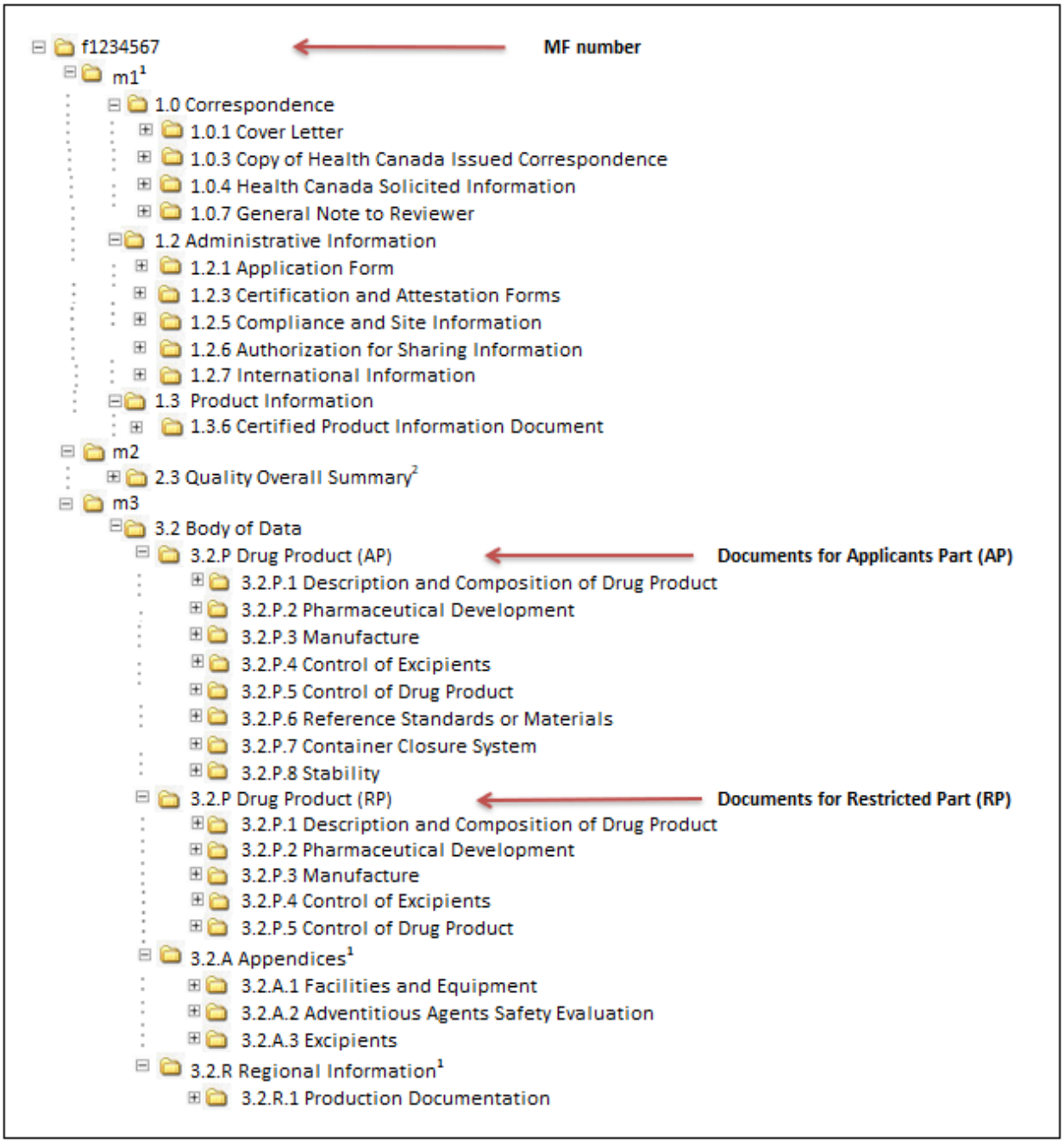


Figure C-4: MF Type IV – Drug Product



1. All documents in this folder will be considered Restricted Part (RP) of the MF.
2. Two separate documents (both in pdf and word format) should be submitted in the folder "2.3 Quality Overall Summary," a "QOS (RP)" and a "QOS (AP)" file.
3. (AP) or (RP) should be used in the subfolder names to identify if the folder is Applicants Part or Restricted Part.

Appendix D: Distribution of master file information between the applicant and restricted parts

Table D-1: MF Type I – 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	-	√
1.0.3	Copy of Health Canada Issued Correspondence	-	√
1.0.4	Health Canada Solicited Information	-	√
1.0.7	General Note to Reviewer	-	√
1.2	**Administrative Information**		
1.2.1	Application 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			
3.2	**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	-	√
3.2.S.2.6	Manufacturing Process Development	-	√
3.2.S.3	**Characterisation**		

Module/ Folder Names		Proposed 2015 Applicant's Part	Proposed 2015 Restricted Part
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.

Table D-2: MF Type IV - Drug Products

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	-	√
1.0.3	Copy of Health Canada Issued Correspondence	-	√
1.0.4	Health Canada Solicited Information	-	√
1.0.7	General Note to Reviewer	-	√
1.2	**Administrative Information**		
1.2.1	Application 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			
3.2	**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*	-	√
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	-	√

Module/Folder Names		Proposed 2015 Applicant's Part	Proposed 2015 Restricted Part
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**		
3.2.R.1.1	Executed Production Documents	-	√
3.2.R.1.2	Master Production Documents	-	√

('**√**' = 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 E: Veterinary Drug Dossier sample folder structures

To compile veterinary drug dossiers, use the structure prescribed in "Appendix V: Master Index" of the Guidance document: Guidance for Industry Preparation of Veterinary New Drug submissions.

Section 1.12 submission and product summary can be used to place documents such as PSUR, meeting package, meeting slides, meeting minutes, and drug notification form.

Figure E-1: Veterinary Pre-Submission Meeting Request transaction

Figure E-2: Veterinary Response to a Clarification Request transaction

Figure E-3: Veterinary PSUR transaction

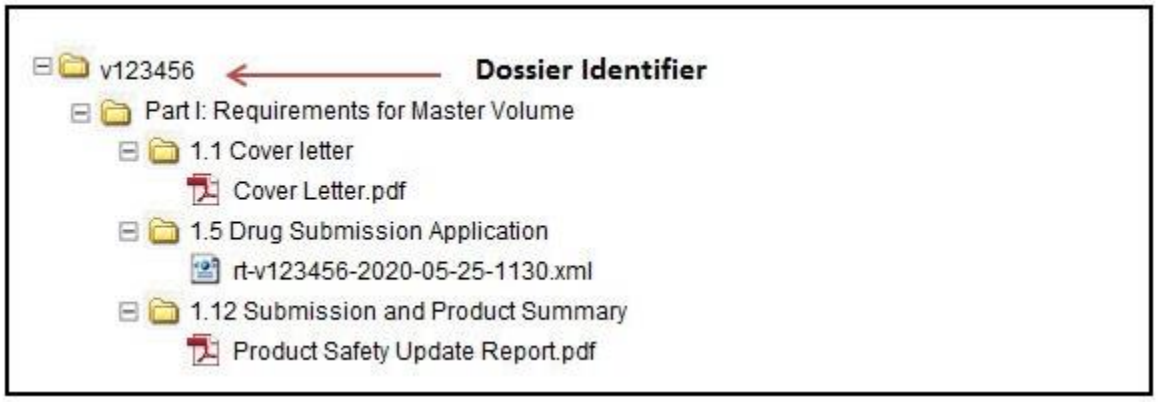
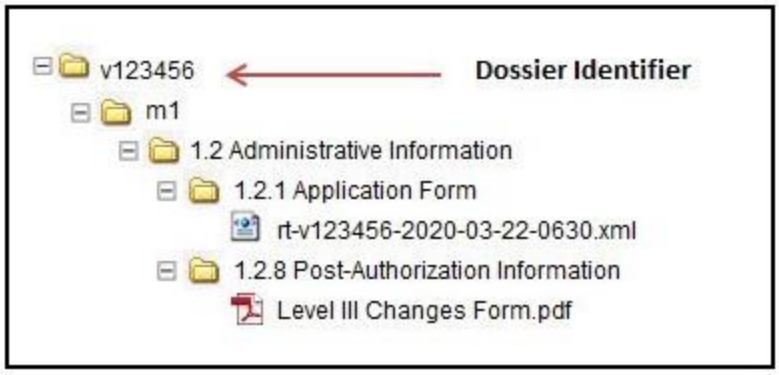


Figure E-4: Veterinary Level III Changes Form Transaction



Appendix F: Common Electronic Submission Gateway (CESG)

The Common Electronic Submissions Gateway (CESG) is a method of securely providing regulatory transactions to Health Canada.

There are two methods for sending transactions:

1. Using FDA Electronic Submission Gateway (ESG) Web Interface (WebTrader)
2. Using Applicability Statement 2 (AS2) Gateway-to-Gateway

To determine which method best fits your company's business requirements, regulatory activity types, and infrastructure capabilities, please visit Section 3.5 of the FDA's User Guide.

This Appendix provides information on how to set up and use a WebTrader. If your company is considering an AS2, refer to FDA's User Guide.

FDA's gateway website.

Step 1: Registering as a trading partner FDA

Registration is required for each WebTrader account and the account user will need to complete the FDA ESG registration process using the ESG Account Management Portal.

The Accounts Management Portal application has been developed to enhance Industry's user experience with onboarding external Electronic Submissions Gateway (ESG) accounts. It automates Industry account registration and approval process to streamline account onboarding and reduce onboarding time. It allows single access to multiple ESG environments and provides Account Management self-service functionality such as password resets, certificate updates or uploads. It also allows Industry power users to manage user accounts and track submission status.

ESG Account Management Portal

ESG Account Portal User Guide

FDA has put together a convenient checklist, with the activities and requirements for companies preparing to setup a WebTrader account(s).

The registration steps are:

1. Preparatory Activities
    - Read the following materials
        - ESG Account Management Portal User Guide
        - ESG User Guide
        - Tutorials
        - WebTrader System Requirements
    - Prepare an electronic Letter of Non-Repudiation Agreement
    - Obtain a Digital Certificate
2. Register your WebTrader test account using the FDA ESG Account Management Portal
3. Setup your computer for ESG
4. Log in to the WebTrader Test website
5. Send "test transaction" – Test transaction is required when setting up all new user accounts. You are required to send a TXT (sample.txt) file to the HC (Health Canada) center using your WebTrader test account (Figure F-1). The content of the TXT files are not reviewed. Once you send the TXT file, you should receive the following two messages:
    - The first is the Message Disposition Notification (MDN)
    - The second is the Acknowledgement containing the Message ID and the Core ID.
6. Wait for FDA to migrate your account.
7. After your test account is migrated, you are ready to send electronic transactions to Health Canada using the production ESG WebTrader application.

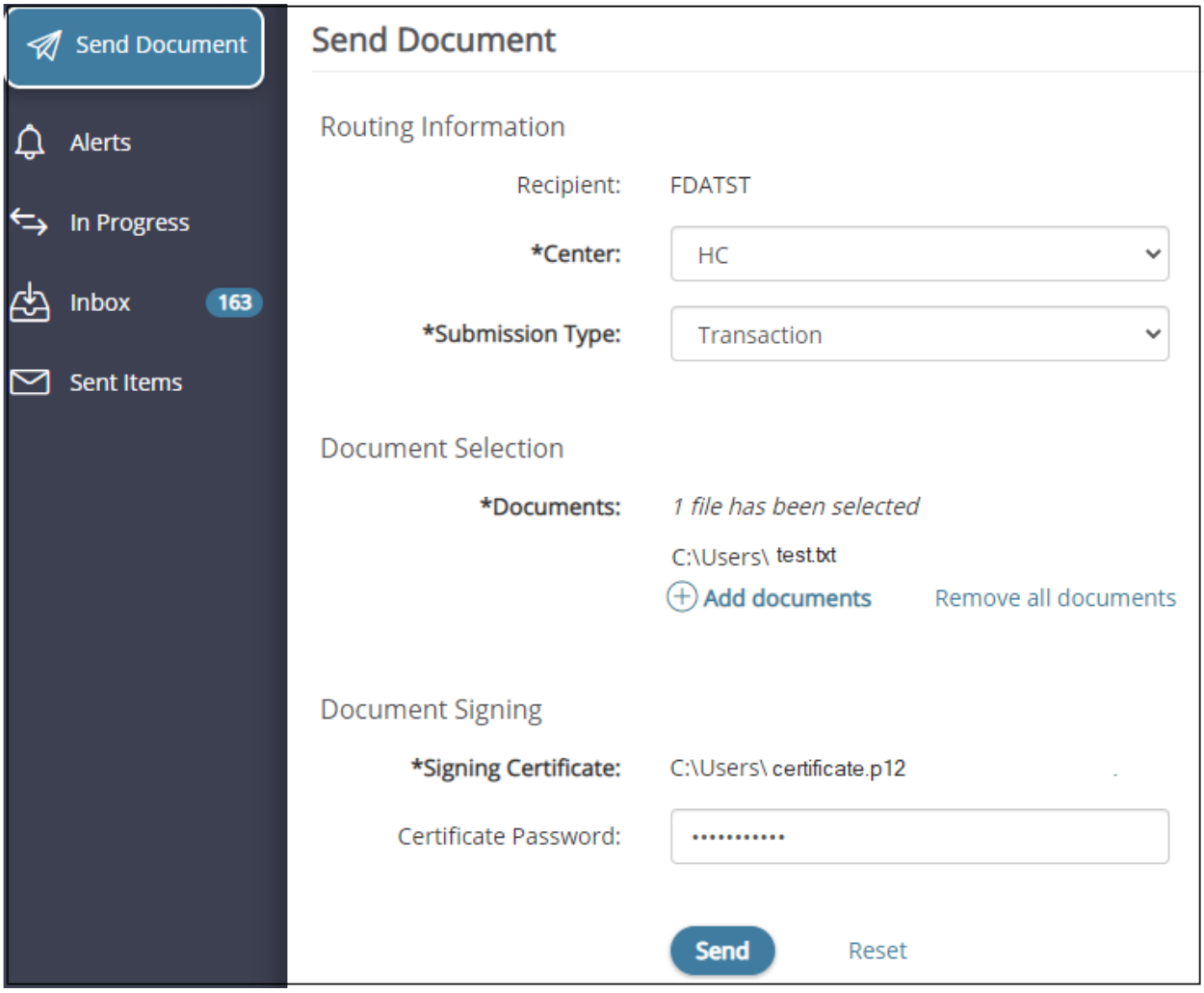
Note: The test transaction must not be sent via the production WebTrader application.

The WebTrader "Routing Information" fields for a test transaction should be filled out as below and as per figure F-1:

- Recipient: FDATST
- Center: HC

- Submission Type: Transaction

Figure F-1: WebTrader Information for sending a sample



The registration process is handled entirely by FDA, and therefore questions at this stage of the process should be directed to the FDA's Help Desk, at ESGHelpDesk@fda.hhs.gov.

Step 2: Sending transactions

After an account has been migrated to production, you may begin to send transactions to Health Canada.

Login to FDA Production WebTrader and navigate to the "Send Document" tab.
Fill out the "Routing Information" fields, as per below:

- Recipient: FDA*
- Center: HC
- Submission Type: Transaction

*__Important:__ once the test account has been migrated to production, the test account will also remain active and therefore each user can send transactions using the test gateway or production gateway. You will need to verify the Recipient information before sending your production transaction to ensure it is FDA. Health Canada is not checking the test environment, therefore any production transactions accidently sent via the test gateway (FDATST) will not be processed.

When selecting a document using the browsing tool, it is helpful to first place a temporary, ready to be sent copy of the whole transaction to a folder in an easy access location, such as your desktop. The top-level folder **must** be named with the "dossier ID" for the regulatory transaction (refer to figure F-2).

Below is a list of each dossier type and the lowercase letter associated with each type, along with the numeric digits to form the dossier ID:

Master Files (MF) Dossier ID: Lowercase letter 'f' followed by a seven-digit identifier (e.g. f1234567)

Medical Devices Dossier ID: Lowercase letter 'm' followed by a six-digit identifier (e.g. m123456)

Veterinary Drugs Dossier ID: Lowercase letter 'v' followed by a six-digit identifier (e.g. v123456)

Pharmaceutical / Biological Dossier ID: Lowercase letter 'd' (Div. 1) followed by a six-digit identifier (e.g. d123456)

Figure F-2: Examples of top level folders for various dossier types

Important considerations:

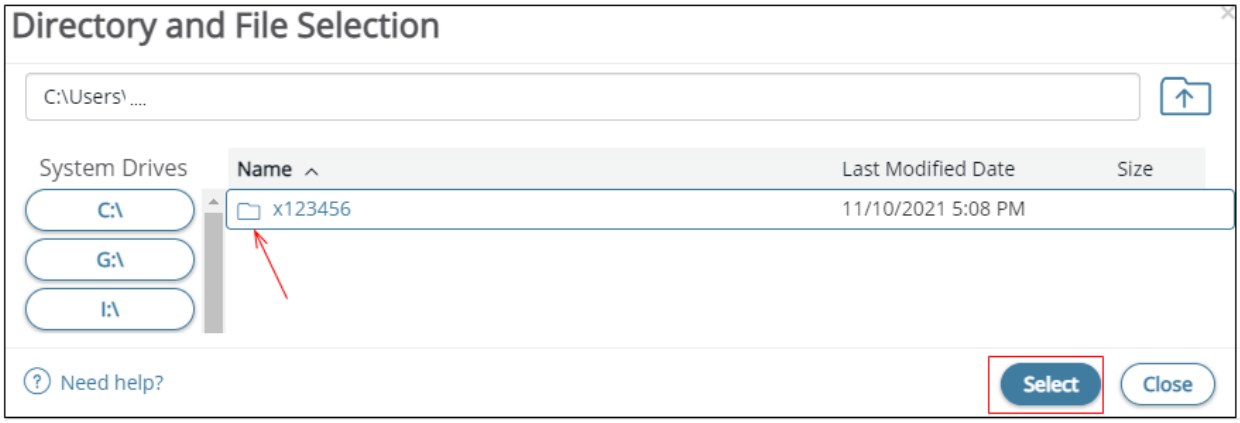
- This step applies to all regulatory transactions; be it the first, or the sixth, seventh, eighteenth, etc. It is important to always create a copy of the regulatory transaction you wish to file, and paste **just that one transaction** inside a folder named with the appropriate dossier ID. Attaching a transaction from a folder containing multiple transactions will result in you sending them all to Health Canada, which will result in a failed transaction.
- Information provided in previous transactions **must not** be provided again, unless it has been changed (i.e.: a MF update, MF letter of access, administrative change, response to NON, response to NOD, response to SDN, etc.).

- Loose files sent via CESG are not accepted by Health Canada. Please refer to the guidance document applicable to your regulatory activity type for instructions on folder structure and file placement.

Once you have located the folder named with the dossier ID, first click on the folder icon, **not on the folder name**, and after click the 'Select' button. Refer to the Figure F-3.

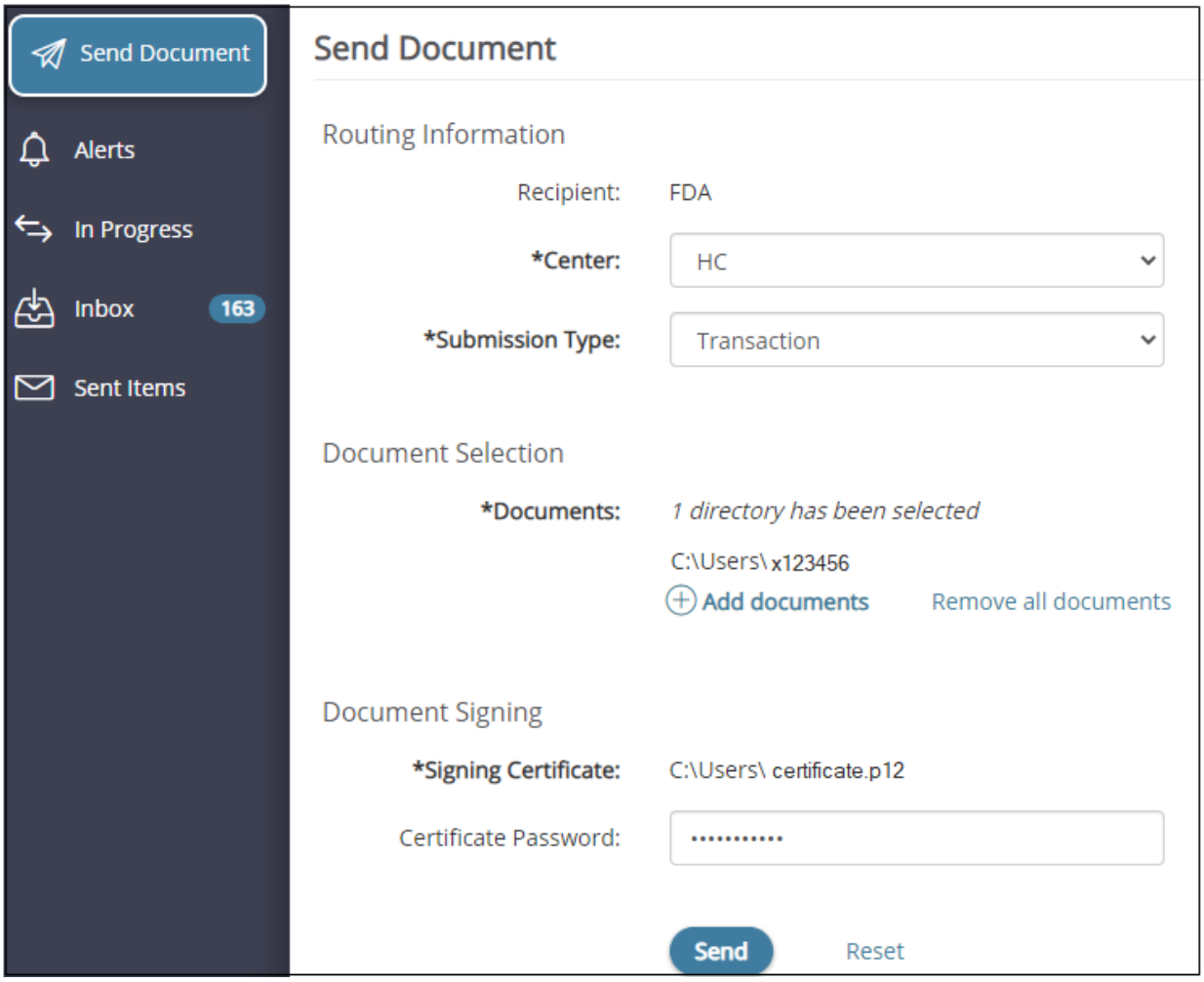
Important: Clicking on the folder name (dossier ID), instead of the folder icon, will drill down an extra level and will send the transaction to Health Canada without the top-level folder. Transactions received without a top-level folder will fail validation and the company will have to resend a corrected transaction via the CESG.

Figure F-3: Directory and File Selection



After clicking the "Select" button, you will be redirected to the main "Send Document" tab. Here, you will be required to retrieve your Signing Certificate and enter you Certificate Password.

Figure F-4: WebTrader Information for sending a transaction



When complete, click the "Send" button. You should then see a green bar that reads: "Your upload has been added to the queue. Completed uploads can be viewed in your "Sent Items" folder."
From here, navigate to the "Sent Items" tab. You must wait to see 'Receipt' and '2 Acknowledgements' next to the Delivered indicator, as confirmation that your regulatory transaction has been received by Health Canada. Refer to figure F-5.

Figure F-5: Sent Items tab

Note: If you do not receive the Receipt confirmation or either of the two Acknowledgements, after a few hours, please email the Health Canada eReview team, at ereview@hc-sc.gc.ca.