Health Canada Santé Canada

Guidance Document

Master Files (MFs) - Procedures and Administrative Requirements

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Canada

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Document change log

Version	Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements	Replaces	Guidance Document - Master Files (MFs) – Procedures and Administrative Requirements
Date	June 26, 2023	Date	January 1, 2021

Change	1) May 1, 2017 Some revisions throughout the document
Nature of and/or Reason for Change	The revised guidance document is administrative in nature and was developed to facilitate information sharing initiatives that are ongoing in collaboration with the International Generic Drug Regulators Programme (IGDRP). These initiatives include bringing efficiencies to MF practices. The document also introduces process changes that are less cumbersome on industry and Health Canada.
Change	2) January 2, 2019 Some revisions throughout the document
Nature of and/or Reason for Change	The revised guidance document is administrative in nature and was revised for the purpose of increasing clarity with respect to the filing requirements for Master File Transactions.
Change	3) December 1, 2021 Introduction of Type V Master Files - Facilities and Equipment
Nature of and/or Reason for Change	The revised guidance document is administrative in nature and was revised to: introduce a new type of Master File for information relating to Facilities and Equipment (MF Type V); outline changes regarding paying fees for Master File transactions; outline the filing requirements for non-substantive changes to company information; and for the purpose of increasing clarity with respect to the filing requirements for Master File Transactions.
Change	4) June 26, 2023 Changes to accommodate the implementation of XML web-based application process.

Nature of and/or Reason for Change	The revised guidance document is administrative in nature and was revised to include the change to an online web-based XML application process.

Note about guidance documents in general

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, in 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 accompanying notice and the relevant sections of other applicable guidance documents.

Table of Contents

1. Introduction

A master file (MF) is a reference that provides information about specific processes or components used to manufacture, process or package a drug. The MF is a useful vehicle for providing information to Health Canada, where that information is confidential business information (CBI) and is not available to the:

- manufacturer of the dosage form or
- sponsors of a drug submission or
- applicants of a DIN (drug identification number) application or clinical trial application (CTA)

Health Canada must protect confidential business information in accordance with the law.

This guidance document provides MF-related definitions, information on filing requirements, processing and assessment procedures for Type I to V MFs. It also outlines the registration requirements for new MFs, as well as other MF transactions including administrative changes, updates, withdrawals and closures.

1.1 Policy Objective

The policy objective is to provide direction on the procedures that allow MF holders, authorized MF agents and authorized third parties filing on behalf of MF holders to file CBI directly with Health Canada. The CBI referenced is in support of an applicant's drug submission (including DIN applications) or CTA with respect to quality information.

Note: 'MF holder' includes authorized MF agent and authorized third parties filing on behalf of the MF holder. This term is used throughout this guidance document.

1.2 Policy Statements

MFs are categorized as regulatory transactions.

For more information, consult:

- Guidance document: Preparation of regulatory activities in non-eCTD format
- Guidance document: Preparation of regulatory activities in the electronic common technical document (eCTD) format

Master files are voluntary registrations filed with Health Canada. They can be referenced by applicants seeking drug marketing authorizations or clinical trial authorizations involving pharmaceuticals and biologics.

Applicants are responsible for submitting non-confidential business information provided by the MF holder. This information is public and/or developed by the applicant in the drug submission, DIN application or CTA.

The information included in the MF should be up-to-date. Applicants should also contact the MF holder to confirm that Health Canada has received this information before filing their submission, DIN application or CTA with us.

The restricted part of the MF will be held in strict confidence. Health Canada will used it in support of the drug submission or CTA only when we have received a written letter of access (LoA) from the MF holder.

The LoA is signed by the MF holder. It indicates to Health Canada that the applicant and MF holder have agreed that the MF can be referred to during Health Canada's assessment of the drug submission or CTA.

1.3 Scope and Application

This guidance document applies to all MF holders or applicants that use an MF to support drug submissions and DIN applications for human use or CTAs. It also applies to Health Canada employees involved in MF processes.

Submissions and applications include the following:

- extraordinary use new drug submission (EUNDS)
- new drug submission (NDS)
- new drug submission with flexibilities for designated COVID-19 drug (NDS-CV)
- abbreviated new drug submission (ANDS)
- abbreviated EUNDS (AEUNDS)
- supplements
- applications for DINs (DINA and DINB)
- post-DIN changes for pharmaceuticals (PDC)
- notifiable changes (NC) (in the case of biologics)
- post-authorization Division 1 changes for biologics (PDC-B)
- yearly biologic product reports (YBPR)
- CTAs, CTA-notifications (CTA-N) and CTA-amendments (CTA-A)

MFs may be referenced by more than 1 applicant.

The guidance document also applies to MF holders intending to file MFs that are cross-referenced in drug submissions and DIN applications for products for both human and veterinary use or CTAs.

For information on the requirements for MFs related to veterinary drug products and substances, consult:

- Guidance document: Master files for veterinary products: Procedures and administrative requirements

The guidance document does not apply to MFs used in support of natural health products (NHPs) subject to the *Natural Health Products Regulations*. For NHP MFs, contact the Natural and Non-prescription Health Products Directorate (NNHPD) at nnhpd.consultation-dpsnso@hc-sc.gc.ca.

MFs are classified according to the types listed in Table 1.

Table 1. Master file classifications

Type of Master File	Description
Type I Active substance master files (ASMFs)	For pharmaceuticals: Active pharmaceutical ingredients (API) (drug substances), starting materials or intermediates used to manufacture a drug substance. For biologics: Drug substances can include bulk process intermediates, vaccine antigens, adjuvants (except for alum), albumin (except when used as an excipient) and critical raw materials for radiopharmaceuticals or vectors for gene therapy.
Type II Container closure system master files (CCS MFs)	Container closure systems (CCS) or CCS components.
Type III Excipient master files	All excipients including those of biological origin (such as albumin), capsule shells, coating ingredients, colourants, flavours and other additives (such as gelatin, alum and growth media).
Type IV Dosage form master files (dosage form MFs)	Dosage forms and drug product intermediates.
Type V Facilities and equipment master files (FMFs)	Diagrams illustrating manufacturing flows (including movement of raw materials, personnel, waste and intermediate(s) in and out of the manufacturing areas, for example). Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product. Information on procedures (such as cleaning and production scheduling) and design features of the facility (such as area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for preparing cell banks and product manufacturing take place.

1.4 Definitions

Active pharmaceutical ingredient (API): Refer to the definition for 'drug substance'.

Applicant: The company submitting a drug submission, DIN application or CTA. This may or may not be the dosage form manufacturer (also referred to as the sponsor).

Applicant's part: The non-confidential business information contained in an MF, formerly called the open part (refer to the information on Health Canada master files).

Authorized MF agent: Any person appointed by the MF holder to file an MF or serve on behalf of the MF holder. The authorized MF agent may file MF-related transactions and/or sign documents on behalf of the MF holder. An authorized MF agent appointment letter signed by the MF holder is required with the initial MF registration transaction or any transaction where a new agent is appointed or the agent's role has changed.

Bovine/transmissible spongiform encephalopathy (BSE/TSE) declaration: A confirmation/attestation of whether the materials used during the manufacture of the product are susceptible to contamination with agents that may transmit BSE/TSE and that the risk of transmitting agents of animal spongiform encephalopathies has been minimized.

Confidential business information (CBI): In respect of a person to whose business or affairs the information relates, means (subject to the regulations) business information:

a) that is not publicly available

b) in respect of which the person has taken measures that are reasonable in the circumstances to ensure that it remains not publicly available and

c) that has actual or potential economic value to the person or their competitors because it is not publicly available and its disclosure would result in a material financial loss to the person or a material financial gain to their competitors

(*Food and Drugs Act*)

Cover letter: A letter accompanying an MF transaction that explains the purpose and content of the transaction provided to Health Canada.

Dosage form: A pharmaceutical product type (for example, tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Dosage form manufacturer: The company that manufactures the finished dosage form.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Drug substance (active pharmaceutical ingredient): Any substance or mixture of substances intended to be used to manufacture a drug product and that, when used in the production of a drug, becomes an active ingredient of the drug product.

Letter of access (LoA): A letter written and signed by the MF holder, authorized MF agent or authorized third party filing on behalf of the MF holder. The LoA indicates to Health Canada that the applicant and the MF holder have agreed that the MF can be referred to during the assessment of the applicant's drug submission or CTA.

Manufacturer: The company that manufactures the product covered by the MF. This may be a manufacturer of a drug substance, container closure system (CCS) or CCS component, an excipient or a finished dosage form.

MF holder: The company that submitted the MF. This may be the manufacturer of the product described in the MF and/or the originator of the CBI.

MF update: A revision or change to any information provided in an existing MF and/or replacement of an existing MF.

Regulatory activity: A collection of all regulatory transactions throughout the process of a specific activity. These include, for example, an NDS, ANDS, DIN application, CTA and yearly biologic product report (YBPR).

Regulatory transaction (sequence): Any information package sent by the applicant as part of a regulatory activity, such as initial data, unsolicited and solicited information.

Restricted part: The CBI contained in an MF, formerly called the closed part (refer to the information on Health Canada master files).

Statement of commitment: A declaration from the MF holder or authorized MF agent that the information provided in the MF is true and accurate.

Third party filing on behalf of the MF holder: Any person acting and/or signing documents and/or managing regulatory activities and regulatory transactions on behalf of the MF holder must be appointed to do so. This is usually done through an MF-authorized third-party authorization letter signed by the MF holder. This letter is required for the initial MF registration transaction or any transaction where a new agent is appointed or the agent's role has changed.

1.5 Background

The principles outlined in this guidance document are intended to create greater alignment with the procedures used internationally for the management of MFs. Extensive knowledge has been gained through international regulatory initiatives such as the International Generic Drug Regulators Programme (IGDRP).

This guidance document also incorporates procedures and terminology from the International Council for Harmonisation (ICH) guidelines and the use of certificates of suitability to the monographs of the European Pharmacopeia (CEPs).

In keeping with international best practices, the term 'master file' (MF) is used. This term was previously known as drug master file (DMF).

2. Guidance for Implementation

2.1 Health Canada Master Files

The MF holder submits a master file (MF) when the company does not wish to disclose confidential business information (CBI) to the applicant of the drug submission, application for a drug identification number (DIN) or a clinical trial application (CTA).

Type I and Type IV MFs are divided into 2 parts:

- "applicant's part"
  - contains information the MF holder regards as non-confidential
  - is provided to the applicant
  - is usually included as part of the applicant's drug submission, DIN application or CTA, with the accompanying letter of access (LoA)
- "restricted part"
  - contains information the MF holder regards as confidential
  - is filed by the MF holder to Health Canada directly

The LoA is signed by the MF holder. It indicates to Health Canada that the MF holder has agreed that the MF can be referred to during the assessment of the applicant's drug submission, DIN application or CTA.

2.1.1 Confidentiality

Health Canada keeps the restricted part of the MF confidential. We must protect the information in accordance with applicable law, which includes the Access to Information Act and the Food and Drugs Act.

The *Access to Information Act* applies where an access request is made under that Act for records under the control of a government institution. Section 20 of the Act is a mandatory exemption. This exemption protects:

- third-party information such as trade secrets
- confidential financial, commercial, scientific or technical information
- information that if disclosed could cause financial loss or gain or prejudice to the competitive position of a third party
- information that could interfere with contractual or other negotiations

Confidential business information contained in an MF could also be subject to the disclosure authorities in the *Food and Drugs Act*. Section 21.1(2) authorizes the disclosure of CBI about a therapeutic product where the Minister believes the product may present a serious risk of injury to human health. Section 21.1(3) of this Act authorizes the disclosure of CBI about a therapeutic product to a government, a person from whom the Minister seeks advice or eligible persons for the purpose of protecting or promoting human health or safety.

Consult the following guidance document:

- Disclosure of confidential business information under paragraph 21.1(3)(c) of the Food and Drugs Act

2.1.2 Registration Requirements

The web-based XML Master File Application Form (MF application form) must be provided with every electronic common technical document (eCTD) and non-eCTD transaction that is sent through the Common Electronic Submissions Gateway (CESG).

MFs should be filed no more than 1 year, but no less than 2 months before a drug submission, DIN application or CTA that refers to those MFs is filed. All MFs must include at least 1 LoA at the time of filing.

An MF number is assigned at the end of the registration process. Thus, any LoAs submitted at the time of registration should include “MF number unassigned” on the LoA. The LoA should not be refiled at a later date to include the MF number.

Learn more about the filing requirements for LoAs.

Any LoAs refiled to include the MF number will be subject to fees.

For new MF registrations, include the following electronic documents:

- 1 signed cover letter, stating the MF name and MF holder name
- MF agent authorization letter from MF holder, if applicable
    - When to file a new master file registration
    - MF agent or third-party authorization letter (sample)
- MF application form
- BSE/TSE declaration
- statement of commitment
- CEP and attestations (for Type I MFs only), if applicable
- letters of access (LoA)
    - Sample letter of access

Note: MFs will be placed on “process hold” until the MF is considered complete.

*The MF application form should include the MF holder’s business address or headquarters address. The address provided on the form will be considered the MF holder’s billing address. All invoices and account statements will be sent to this address.

Manufacturing site addresses should not be provided on the MF application form unless the is the same as the business or headquarters address.

The address **must be the same for all MFs held by the MF holder, including subsequent transactions for such MFs.** It is not possible to provide MF application forms with different addresses for different MFs or for different transactions. If the address that the MF holder enters on the MF application form is not the same as what was previously provided for other transactions for MFs held by the MF holder, the MF Administration Unit will issue a process hold letter to resolve any discrepancies.

Type I and IV MFs should include the following:

- applicant part and restricted part
- a copy of a quality overall summary (QOS) in Microsoft Word **and** portable document format (PDF)
- the certified product information document (CPID) in Microsoft Word
    - the CPID template can be adapted to provide only the sections relevant to the manufacture and control of the drug substance

For Type II and Type III MFs, multiple components may be included in a single MF provided they are similar (for example, a complete container closure system, different stopper formulations, multiple flavours). A limit of 50 components will be enforced for each MF. A numbered index listing all components should be included with the MF in Module 1, Section 1.0.7 Note to Reviewer. Additional components should be filed in a new MF.

An MF filed in support of a CTA may include a quality overall summary (QOS) in place of the applicant part and restricted part. As well, a single MF covering both an active substance (Type I MF) and dosage form (Type IV MF) can be filed in support of a CTA.

Of note, MFs will only be reviewed with an applicant's drug submission, DIN application or CTA for which an LoA was provided. Health Canada does not authorize the MF unless a DIN, notice of compliance (NOC) or no objection letter (NOL) is issued for the associated drug product. **Health Canada does not have a database that lists all MFs registered in Canada.**

A single MF may contain information on different products or a family of products. Type I MFs may contain information on different products in accordance with "when to file a new MF registration".

Type II and III MFs may contain information on different products within a family of products (for example, for stoppers manufactured using the same formulation).

Type IV MFs may have more than 1 product strength with the same formulation except for changes necessary to accommodate the different strengths. In such cases, the information for each product should be clearly differentiated within the Type IV MF.

Type V MFs may contain information on different processes (for example, sterilization, cleaning) for products, or a family of products, manufactured at the same facility. Information for each process should be clearly differentiated within the Type V MF.

If the MF holder has more than 1 MF for a similar product, the cover letter should state this. A table comparing the different products should be created and placed in Module 1.0.7, General Note to Reviewer. The MF holder should provide a name that distinguishes the MF from any previously registered MFs.

2.1.3 Naming a Master File

For Type I MFs, the preferred name of the MF should be the generic name (for example, the international non-proprietary name, or INN, for an active pharmaceutical ingredient, or API) followed by any manufacturer's internal API brand names, processes or codes to identify a particular product. If applicable, any counter ions or solvated states of the API should be clearly identified.

2.1.4 Format and Structure of the Master File

All MF transactions must be filed using the Common Submission Electronic Submission Gateway (CESG) in the non-eCTD or eCTD format as appropriate.

For more information on submitting MF Transactions using the CESG, please refer to:

- Filing submissions electronically

MFs in the eCTD format:

Since January 1, 2020, new MFs have been filed in the eCTD format as per the structure and formatting requirements.

Consult the following guidance document:

- Preparation of regulatory activities in eCTD format and Common Electronic Submissions Gateway (CESG)

Existing MFs can also be converted to the eCTD format (refer to next section on converting).

First-time MF holders: Contact eReview at ereview@hc-sc.gc.ca before filing any type of MF in eCTD format.

MFs in the non-eCTD format:

Regulatory transactions (for example, updating a registered MF, LoAs, administrative changes) for existing MFs, where an MF number and dossier ID have already been assigned, are accepted in the non-eCTD format.

For structure and formatting requirements for MF transactions in the non-eCTD format, consult the following guidance document:

- Preparation of drug regulatory activities in the non-eCTD format

2.1.4.1 Converting MFs from non-eCTD Format to eCTD Format

MF holders or authorized MF agents may also convert their MFs from the non-eCTD format to the eCTD format. As a baseline requirement when converting MFs from the non-eCTD format to the eCTD format, the MF holder or authorized MF agent must include a copy of the entire MF in their first eCTD transaction. Any changes/updates filed with a conversion will be subject to update fees.

Include the following documents with a conversion:

- new cover letter outlining the purpose of the transaction
- new signed and dated MF application form
- authorized MF agent or third-party appointment letter, if applicable
- statement of commitment
- BSE/TSE declaration
- CEP and CEP attestations, if applicable
- copy of all previously authorized LOAs

- certified product information document (CPID), if applicable
- quality overall summary (QOS) in both Microsoft Word and PDF format in Module 2, if applicable
- chemistry and manufacturing data in Module 3

Do not include:

- previously submitted cover letters
- previous Health Canada-issued correspondence, such as clarification requests, deficiency letters, emails
- previously submitted responses to clarification requests or responses to deficiency letters, such as questions and answers format
- previously submitted MF application forms
- previously submitted MF application fee forms
- earlier versions of the CEP

It is not enough to convert the MF into the eCTD format by simply submitting the next transaction in eCTD using the CESG. For example, do not submit an LoA or update in eCTD format as a subsequent transaction for an MF currently in non-eCTD format.

2.1.4.2 Master Files in Paper Format

Health Canada will no longer assess MFs that have not yet been converted into non-eCTD or eCTD format. We will also not accept updates and cross-references.

We will suspend the MF until the MF holder submits a cover letter to us along with a copy of the complete MF in the non-eCTD or eCTD format (including any applicable updates since the date of suspension or closure). **The same MF number will be retained and fees for a new MF registration will be applied.**

2.1.5 Official Language of Correspondence

An MF may be filed in either of Canada's official languages (English or French).

2.1.6 Letter of Access (LoA)

MF holders or authorized MF agents file confidential business information (CBI) directly with Health Canada. The information may be referenced to support an applicant's drug submission, DIN application or CTA with respect to quality information. Health Canada will only use this information to assess the applicant's drug submission, DIN application or CTA if the MF holder provides a signed letter of access (LoA) on official company letterhead. All LoAs are valid throughout the life cycle of an MF.

A list of authorized applicants is an administrative document. It does not grant an applicant access to an MF. Access is granted through an LoA that:

- has been received by Health Canada
- is considered administratively complete (in the proper format, for example)
- fees have been paid
- an acknowledgement letter for information received has been issued

Any applicants listed on the list of authorized applicants for which a signed and dated LoA has not been received by Health Canada, or for which an LoA is not considered administratively complete, will not be granted access to the MF.

2.1.6.1 Information to include in the Letter of Access

Include the following information in the LoA:

- MF number, if assigned by Health Canada
  - if not yet assigned, state "to be assigned"
- name of the MF
- applicant's name and address being granted access to the MF

Do not include:

- product name or line
- submission type or number

2.1.6.2 Sample Letter of Access

The applicant's name on the LoA should be the same as the company name on the application form submitted by the drug sponsor with their drug submission. LoAs naming third parties filing or managing regulatory activities on behalf of the applicant will not be considered acceptable. Only 1 applicant can be named for each LOA.

Note: "Affiliates" constitutes multiple entities and will not be accepted on an LoA.

A list of authorized applicants is not required to be submitted with MF transactions for LoAs. If such a list is provided, it will not be verified to validate that all listed applicants have access to the MF.

2.1.6.3 Filing a Letter of Access

A separate LoA is required for each applicant who cross-references the MF in their drug submission, DIN application or CTA.

Each LoA must be:

- accompanied by an MF application form and is subject to the applicable fees
- dated and signed by the MF holder or authorized MF agent

The LoA should be sent to the MF Administration Unit in the eCTD or the non-eCTD format using the CESG and to the applicant before they file their drug submission, DIN application or CTA.

LoAs provided to the applicant **must be identical** (have the same date, same letter, same content, same signature) to those provided to the MF Administration Unit. Any discrepancies between LoAs provided to the applicant and those provided to the MF Administration Unit may delay Health Canada's assessment of the drug submission, DIN application or CTA. This is why we recommend that MF holders wait to receive an acknowledgement letter for information received from the MF Administration Unit for any LoAs before they provide applicants with a copy of the LoA.

As an MF number is assigned at the end of the registration process, any LoAs submitted at the time of the initial new MF registration should include “MF number unassigned” on the LoA. The LoA should not be revised and/or refiled at a later date to include the MF number. Any LoAs refiled to include the MF number or to change information will be subject to additional fees.

For Type I, IV and V MFs, an LoA grants access to an MF in its entirety. The LoA is valid for all products and submissions from the applicant that cross-reference the MF. Therefore, only 1 LoA is required per applicant for the duration of an MF’s lifetime.

For Type II and III MFs, an LoA can grant access to specific components within an MF or an MF in its entirety. When granting access to multiple components within the MF or the MF in its entirety, only 1 LoA is required per applicant for the duration of the MF’s lifetime. When granting access for an additional component that is not included in the first LoA, a new LoA is required with the applicable fee.

MFs can also reference other MFs and be referenced by other MFs. In such cases, MF holders or authorized MF agents must file an LoA granting access to their MF to another MF holder. For example, when a Type IV MF references a Type I MF, the Type I MF holder or authorized MF agent must file an LoA granting access to the Type IV MF holder. Separate LoAs must also be filed granting the applicant access to the Type I and IV MFs.

The fee for processing an LoA is applicable each time an LoA is filed. LoAs should only be revised and refiled when the applicant's name is changed. In these cases, MF holders will be charged the applicable fees. If the MF holder is changing their company name, the MF holder or authorized MF agent may submit a letter stating that their name has changed but that all previous LoAs (issued under previous MF holder name) are valid. No fees will be applied for a name change where no new LoAs are issued.

Please contact the MF Administration Unit before refiling an LoA to confirm requirements.

Note: The declaration of access section in the CEP is not equivalent to an LoA. Furthermore, the CEP or a copy of the declaration of access section in a CEP should not be submitted with each LoA.

2.1.6.4 Letters of Access for Clinical Trials (Pharmaceuticals and Biologics)

The LoA should name the sponsor of the CTA and the name of the clinical trial as it appears on the application form submitted with the CTA. LoAs naming third parties to file or manage regulatory activities on behalf of the applicant are not acceptable. Additional information such as hospital information, principal investigator and protocol number can be provided.

2.1.7 Certificates of Suitability to the Monographs of the European Pharmacopeia (CEPs)

At the time of filing of a Type I MF, MF holders are encouraged to include the CEP (as applicable) or confirm on the cover letter for the transaction that no CEP is available. If a CEP is not available when the MF is filed, it should be provided as soon as it becomes available. In this case, no fees will be applied.

If the MF is revised or updated at the same time a CEP is submitted, applicable fees will apply. Revised CEPs will be accepted with or without simultaneous updates to the MF.

Send all CEPs to the MF Administration Unit with the relevant attestations. Provide new attestations for revised CEPs and indicate the CEP number in the attestations.

A CEP can be submitted as supporting information for an MF when the MF is not completely identical to the CEP dossier. Even if the MF is different from the dossier submitted to the European Directorate for the Quality of Medicines & HealthCare (EDQM) (for example, USP standard is declared), providing a CEP may expedite the assessment process and avoid unnecessary questions being sent to the MF holder. The attestations can be altered appropriately in this case. Any differences between the MF and the CEP dossier should be clear. We recommend using a table that compares the MF and CEP and providing this table in Module 1.0.7 Note to Reviewer.

Please note that CEPs can also be provided directly in the applicant's drug submission or DIN application instead of providing Active Substance Master Files (ASMFs).

For more information on how to use this alternate procedure, consult the following guidance document:

- Use of certificates of suitability as supporting information in drug submissions

2.1.8 Appointing an Authorized Master File Agent or Authorized Third Party

MF holders may appoint an agent or third party to act on their behalf. This includes signing documents and managing regulatory activities and transactions on behalf of the MF holder. An agent or third party filing on behalf of the MF holder who is appointed by the holder (refer to MF agent or third-party authorization letter sample) is responsible for all correspondence related to the MF. This may include, among other tasks, the following:

- issuing LoAs
- handling deficiencies
- managing the payment of fees
- managing associated correspondence
- filing updates and administrative changes

An MF agent or third-party authorization letter signed by the MF holder is required with the initial MF registration transaction (including conversions) or any transaction where a new agent is appointed or the agent's role has changed.

When the MF holder is not based in North America, to speed up communications, we recommend that an agent or third party filing on behalf of the MF holder be located in North America. Once appointed, an authorized MF agent or third party filing on behalf of the MF holder may perform all functions listed in this guidance document on behalf of the holder.

2.1.9 When to file a New Master File Registration

When 2 or more MFs are being filed for similar active substances and differ only due to additional processing steps or minor variations, include cross-references to the other related MFs in the cover letters. This will speed up the assessment of the common information. Include a table that compares the MFs in Module 1, Section 1.0.7 General Note to Reviewer.

In some cases, a new Type I MF registration is required. The following examples indicate the criteria for new MF registrations:

- different active substance
- different salt of an active substance
- different complex of an active substance
- different co-crystal of an active substance
- different solvate or hydrate form of an active substance
- different isomer or mixture of isomers of an active substance
- racemate of an optically pure active substance
- optically pure enantiomer of a racemic active substance
- enantiomer of an active substance
- introduction of a new very different route of synthesis
    - resulting in a different specification for the active substance
- different polymorphic forms
    - resulting in very different physicochemical and/or pharmacokinetic properties
- any other change to the active substance that results in very different physicochemical and/or pharmacokinetic properties
- sterile grade of a non-sterile active substance
- non-sterile grade of a sterile active substance
- change/addition of raw materials of different animal origin
    - only where there's a substantial change in the safety of the active substance

The following examples do not necessarily represent a new Type I MF and could be incorporated in a single MF with the same MF number:

- slightly different routes of synthesis that do not result in very different physicochemical and/or pharmacokinetic properties
- different manufacturing sites using the same or similar routes of synthesis
    - same specification for the active substance
- different particle size grades
    - should be controlled in the drug product manufacturer's active substance specification
- different container closure system resulting in a different re-test and storage conditions
- other changes that do not result in very different physicochemical and/or pharmacokinetic properties

Consult the relevant program area before submitting the MF if you are not sure if you should submit a separate MF.

2.1.10 Master File Fees

The MF process is voluntary and a private benefit. Thus, non-regulatory charges are fully cost-recovered under the ministerial authority to "enter into contract".

Health Canada collects fees to register and process each new MF, LoA and updates to a registered MF. Note that there's a fee each time an LoA is re-filed.

Any transactions received after 5 pm are considered to be received the next business day. Fees are increased annually by 2% on April 1 each year. If an MF holder responds to a processing/classification hold after 5 pm on March 31, the new fees will apply.

All payments made to Health Canada must be made in Canadian funds. Cheques must be made payable to the Receiver General for Canada.

For instructions on the payment of fees:

- How to pay fees for health products

Do not send payment when you file a transaction. Once Health Canada considers the transaction is administratively complete, we will send an invoice to the designated contact that has been provided (owner or agent).

Payment is due within 30 days from the date of the invoice. Failure to pay an invoice may delay our review of the submission. Access to an MF may be denied. If fees are not paid, Health Canada reserves the right to deny service to MF holders and suspend access to an MF.

If you have questions about the fees for MFs, please email us at cost.recovery@hc-sc.gc.ca.

2.2 Processing Master Files

When Health Canada receives an MF transaction, we:

- assign an MF number and a dossier ID* to the MF (only for new MF registrations)
- verify the correct information, documents and forms have been filed in the correct format and are administratively complete (including those related to cost-recovery)

Note: For MFs submitted in eCTD, the dossier ID is assigned before the new MF registration transaction is received using the Dossier ID request form.

Once the MF transaction is administratively complete, we:

- assign a filing date (the date when the MF is considered administratively complete)
- send an acknowledgement letter (with an MF number and dossier ID) to the designated MF contact person listed on the MF application form:
    - MF holder
    - authorized MF agent
    - authorized third party

If the required information or forms are missing, incomplete or in the incorrect format, Health Canada will place the MF on administrative hold. Our MF Administration Unit will send an administrative process hold letter to the MF contact person asking for the missing information.

Note: A file is administratively complete when:

- all processing and cost-recovery requirements are met
- all required information or forms are provided in the correct format and are complete

2.2.1 Process Holds

During the administrative process, it may be necessary to place the MF transaction on process hold when:

- required information or forms are missing or incomplete
- information is filed as the wrong transaction type (for example, the new MF should have been filed as an update

When the reason for the process hold is addressed, the MF transaction is considered administratively complete and a filing date will be issued.

We will reject the transaction without prejudice if the MF holder fails to respond to a request for additional or corrected information in the prescribed time outlined in the hold letters. If you receive a rejection notice, you must re-file the entire MF transaction, in the applicable format, using the Common Electronic Submissions Gateway (CESG). This means all documents originally filed in the rejected transaction must be resubmitted again, including a new cover letter.

Health Canada will not accept a response to a process hold after the prescribed time, which is outlined in the process hold letter.

As well, if you are refiling a transaction in eCTD format, you must resubmit all documents in subsequent sequence under the same dossier ID (unless otherwise instructed in the rejection letter). Use operation attribute “replace” or method file reuse “replace” (if the content of the refiled documents is not changing).

For help or if you have questions about refiling rejected MF transactions in eCTD format, email us at eReview@hc-sc.gc.ca.

2.2.2 Application and File Maintenance Requirements

All correspondence (such as cover letters or LoAs to an MF) should come from the MF holder, authorized MF agent or authorized third party filing on behalf of the MF holder, where applicable. We will place on process hold any information filed by a third party for which no agent or third-party authorization letter has been received. The file may be rejected if no authorization letter is provided.

All information included in the applicant part of the MF must be provided to the applicant of the drug submission, DIN application or CTA referencing the MF. This information must also be included in submissions or applications to Health Canada.

The contact information of the MF holder should be up-to-date throughout the life cycle of the MF. The holder must inform us of any changes to the contact information (for example, changes to the holder’s name, address or contact person). This ensures that correspondence from Health Canada will be received by the appropriate person.

Failure to receive Health Canada-issued correspondence (such as process hold letters, notices, invoices, acknowledgement letters, emails) due to out-of-date contact information are not valid reasons for failing to respond to solicited information.

For more information on filing changes, refer to the section on administrative changes.

2.2.3 Master File Performance Standards

Health Canada's MF Administration Unit will process all information and material filed with an MF transaction within 30 calendar days of receiving a complete package (the date the MF is considered administratively complete). MF holders are strongly encouraged to register master files or new LoAs at least 2 months ahead of an applicant's drug submission, DIN application or CTA.

2.3 Assessing Master Files

MFs are always assessed along with a drug submission, DIN application or CTA. Decisions about quality-related data in an MF will pertain to the drug seeking market authorization or to the clinical trial authorization.

Note: The requirements of Division 2, Good Manufacturing Practices (GMP) of the *Food and Drug Regulations* apply to all buildings that fabricate, package, label or test active pharmaceutical ingredients (APIs) and dosage forms.

For more information, consult Division 1A and 2 of the Regulations.

For technical requirements of an MF, consult the following guidance documents that apply.

For pharmaceuticals:

- Quality (chemistry and manufacturing) guidance: New drug submissions (NDSs) and abbreviated new drug submissions (ANDSs)
- Addendum - Quality (chemistry and manufacturing) guidance: Questions and answers
- Quality (chemistry and manufacturing) guidance: Clinical trial applications (CTAs) for pharmaceuticals
- Certified product information document: Chemical entities CPID-CE

For biologics:

- Preparation of the quality information for drug submissions in the CTD format: Biotechnological/biological (biotech) products
- Preparation of the quality information for drug submissions in the CTD format: Blood products (archived)
- Preparation of the quality information for drug submissions in the CTD format: Conventional biotherapeutic products (archived)
- Harmonized requirements for the licensing of vaccines and guidelines for the preparation of an application
- Blank certified product information document (Schedule D drugs) (CPID (Schedule D drugs)) template in the CTD format

- Preparation of the quality information for radiopharmaceuticals (Schedule C Drugs) using the quality information summary- Radiopharmaceuticals (QIS-R) and certified product information document- Radiopharmaceuticals (CPID-R) templates

For specific information on the content of Type II, III and V MFs not covered in these guidance documents, contact the relevant program area.

2.3.1 Solicited Information

For Type I MFs, include all non-confidential business information on the drug substance in the drug submission, DIN application or CTA.

Communications concerning the restricted part of the MF during the assessment of an applicant's drug submission or CTA will be kept exclusively between the MF holder and Health Canada officials. Relevant comments about the restricted part of the MF will be forwarded directly to the MF holder in the form of an MF letter of deficiency or a clarification request. Comments on the applicant part of the MF (related to, for example, analytical methods, stability data) may also be forwarded to the MF holder.

If there are deficiencies within the MF's restricted part, we will notify the applicant that outstanding issues must be addressed before the MF is acceptable to support the drug submission, DIN application or CTA. Other applicants cross-referencing the deficient MF (for which a response to the MF letter of deficiency or clarification request has yet to be received) will receive the same notice.

We will not issue a new letter of deficiency to the MF holder unless new comments need to be forwarded (for example, different requirements for APIs used in a different dosage form).

2.3.2 Clarification Requests and Letters of Deficiency during MF Assessment in support of a submission

During the assessment of an MF, if we need any information to be clarified, we will issue a request for this information by email or fax. The MF holder will have 15 calendar days to reply. If the holder does not respond within the given timeframe or if the MF has a significant number of deficiencies, we will issue a letter of deficiency.

The MF holder must respond to the letter of deficiency within the timeframe specified in the letter. If the holder needs more time, they should contact the relevant applicant for the drug submission. The applicant will then contact the director of the relevant assessment bureau to request an extension.

At the time we are deciding on the applicant's drug submission, we will issue a notice of non-compliance (NON) to the applicant if:

- we have not received a response to a letter of deficiency or
- the response is not satisfactory

No additional correspondence will be sent to the MF holder. The holder is, however, expected to respond within the timeframe given to the applicant to respond to the NON.

MF transactions for responses to quality clarification requests and letters of deficiency should only include solicited information. Unsolicited information (for example, new LoAs) filed with a response to such requests or letters may result in an administrative process hold. This may also delay our review of the applicant's drug submission, DIN application or CTA.

2.3.3 Clarification Requests during MF Assessment in support of a CTA

If we require further information during our assessment of an MF in support of a CTA, we will issue a request for clarification within 2 calendar days to the MF holder. The applicant will be notified in writing.

The applicant should ensure that the MF holder responds within the time period. Failure to provide a satisfactory response within the specified period could result in the CTA being withdrawn or a not satisfactory notice (NSN) being issued.

Consult the following guidance document:

- For clinical trial sponsors: Clinical trial applications

2.3.4 Responses to Clarification Requests

For MFs filed in non-eCTD format, responses to clarification requests and letters of deficiencies must be sent to the MF Administration Unit in non-eCTD format through the Common Electronic Submissions Gateway (CESG).

Consult the following guidance document:

- Preparation of regulatory activities in non-eCTD format

Responses to clarification requests or to letters of deficiency that are in the incorrect format will be put on administrative process hold until we receive the response in the correct non-eCTD format through the CESG.

For MFs filed in eCTD format, submit responses as a new sequence through the CESG.

2.4 Updating a Registered Master File

Updates are to be filed by the MF holder and submitted through the CESG. Updates to the MF are not required on a timed basis, but are required when changes are in accordance with the relevant reporting categories. Consult:

- Guidance document on post-drug identification number (DIN) changes
- Guidance document: Post-notice of compliance (NOC) changes: Quality document
- Guidance document for clinical trial sponsors: Clinical trial applications

All updates are subject to fees and should be accompanied by the MF Application Fee Form.

A single electronic copy of the update should be filed with a signed and dated cover letter. The cover letter should clearly indicate:

- MF number
- dossier ID/HC file number
- type of MF (I, II, III, IV or V)

Additional administrative documents include a:

- summary of changes
  - a table comparing the changes to the affected sections of the MF, indicating the level and impact of each change
  - refer to the guidance documents listed at the beginning of this sub-section
  - put in Module 1, Section 1.0.7 General Note to Reviewer
- revised MF application form

Include all affected data in Module 3.

MF holders no longer need to submit a list of authorized applicants with their updates to a registered MF. We still require this list for conversions to the electronic format and with certain administrative change transactions.

The list of authorized applicants is administrative in nature and does not grant an applicant access to an MF. Access is granted through an LoA that Health Canada:

- has received
- considers administratively complete (in the proper format)
- has received the relevant fees
- has issued an acknowledgement letter for information received

We will not grant access to the MF to any applicants on the list of authorized applicants if we have not received a signed and dated LoA.

When filing an update to Type II and III MFs for an additional formulation or component, a limit of 50 components or formulations for each MF will be enforced. Additional components or formulations should be filed in a new MF. Include a current numbered index listing all components or formulations in Module 1, Section 1.0.7 General Note to Reviewer. Highlight in the numbered index which components or formulations are being added to the existing components or formulations.

Only affected sections of an MF should be filed with an update. An entire MF should not be filed with an update unless it is a conversion to the:

- non-eCTD electronic-only format
  - outlined in the guidance document Preparation of regulatory activities in the "non-eCTD electronic-only" format
- eCTD format
  - outlined in the guidance document Preparation of regulatory activities in the electronic common technical document (eCTD) format

For drug submissions and DIN applications:

File updates to MFs when the applicant for an associated submission is required to submit a Level I, supplement (such as a major quality change) or a Level II, notifiable change (in the case of biologics). Include any changes made in the interim period that are considered Level III, annual notifications.

Consult:

- Post-notice of compliance (NOC) changes: Quality document

This does not exempt applicants from reporting Level III changes in their annual report to Health Canada. MF holders or authorized MF agents should communicate these changes directly and in a timely manner to each applicant, referencing the MF.

All changes to an MF should be accompanied by a table that compares the changes to the previous MF. Indicate each change and noted whether the change falls under Levels I, II, III or IV.

Consult:

- Post-NOC changes: Quality guidance document - Appendices 1 to 3

All Level III changes to an MF should be filed when the next Level I or II changes are submitted. While it's not necessary to report Level IV, MF holders should note if Level IV changes are made in the documentation submitted in an MF, for historical purposes.

It's not necessary to provide an update to an MF solely for Level III or IV changes. MF holders may file an update at any time.

Note: Fees for all updates filed with Health Canada will apply.

With respect to DIN products, updates to MFs should be filed when the applicant for the associated application is expected to submit a notification that necessitates an assessment (post-authorization Division 1 change (PDC)).

Consult the following guidance document:

- Post-drug identification number (DIN) changes - Appendix II: DIN submission types - Pharmaceuticals for human use and disinfectant drugs

The MF holder should also notify each applicant that has been granted access to the MF before implementing the change(s). This is so that applicants can update their records and file the appropriate submission or PDC to Health Canada.

Consult the following guidance documents:

- Post-drug identification number (DIN) changes
- Post-notice of compliance (NOC) changes: Quality document

The MF update should be filed and an MF acknowledgement letter should be received by the MF holder before Health Canada receives the applicant's:

- application for the post-DIN change or
- submission for the post-NOC change
    - for example, supplement, notifiable change

For clinical trial applications:

The MF holder should update MFs if the previously filed information is not current. The holder should also notify each clinical trial applicant who has been granted access to the MF of the changes. This is so that sponsors can update their records and file either a CTA-A or a CTA-N to Health Canada.

Consult:

- Guidance document for clinical trial sponsors: Clinical trial applications

The MF update should be filed and an MF acknowledgement letter should be received by the MF holder before Health Canada receives the CTA-A or CTA-N by the clinical trial applicant.

2.4.1 Administrative Changes

Administrative changes to an MF may be filed at any time throughout the life cycle of the MF. There are no fees for filing administrative changes to an MF.

2.4.1.1 Transfer of Ownership and Substantive MF Holder Name Changes

MF holders should advise Health Canada in writing if the:

- holder's company name has changed substantively or
- ownership of the MF has changed due to:
    - buyout
    - merger
    - transfer of ownership
    - corporate restructuring
    - company name change

Substantive administrative changes should be filed to the MF Administration Unit in non-eCTD or eCTD format through the Common Electronic Submissions Gateway (CESG).

File all administrative changes with a signed and dated cover letter. In the cover letter include the following:

- MF number
- dossier ID
- MF type
- name and address of the new MF holder
- reason for administrative change (for example, transfer of ownership, company name change)
- list of all affected MFs

- confirmation that all LoAs are valid
- confirmation that all manufacturing sites and processing are the same
- confirmation that the previous authorized MF agent or authorized third party filing on behalf of the MF holder is still valid, if applicable

Health Canada also requires the following documents:

- for new MF holders, a letter accepting transfer of ownership (doesn't apply for a company name change)
    - include in Module 1, Section 1.2.9 Other Administrative Information
- proof of company name change (incorporation or certificate of continuance)
    - include in Module 1, Section 1.2.9 Other Administrative Information
- revised MF application form
- current list of all applicants authorized to access the MF
    - include in Module 1, Section 1.2.6 Authorization for Sharing Information for each MF

Health Canada will place on administrative process hold any transactions for transfers of ownership that are not accompanied by a transfer of ownership letter until this letter is provided.

When multiple MFs are affected by an administrative change, a transaction is required for each MF. For example, if a company name change affects 10 MFs, we require 10 administrative changes to be filed (1 for each MF).

2.4.1.2 Non-substantive Changes to MF Holder Contact Information

MF holders should advise us in writing of any non-substantive changes to their address or MF contact person.

Note: We may consider minor non-substantive name changes to the MF holder if the name of the holder is largely the same (for example, "Limited", "Ltd", "Incorporated" or "Inc." has been added or removed). Contact the MF Administration Unit if you are not sure whether an MF holder name change is considered non-substantive.

Non-substantive changes to an MF holder's contact information should be sent to the MF Administration Unit by email at dmf.enquiries-fmm@hc-sc.gc.ca. There is no need to inform us of such changes through the CESG.

Include a cover letter that contains the following information:

- MF number
- dossier ID
- MF type
- reason for administrative change
    - for example, non-substantive MF holder name change, change in address, new MF contact person
- list of all affected MFs

Health Canada will send an acknowledgement letter to the MF holder after the holder files non-substantive changes to the MF holder's information.

All subsequent MF transactions must accurately reflect the changes to the MF holder's information in the MF application form. If the MF application form for subsequent transactions does not reflect the approved changes, we will issue an administrative process hold letter.

2.4.1.3 Change of Authorized Master File Agent or Authorized Master File Third Party

If a company wishes to change the current authorized MF agent or authorized master file third party, the MF holder should send a letter to the MF Administration Unit in the proper non-eCTD or eCTD format through the Common Electronics Submission Gateway (CESG).

The MF holder must make sure that the new appointee has all the information required (such as historical records). Health Canada is not responsible for providing duplicate information to a new appointee.

2.5 Withdrawing Letters of Access

MF holders who wish to withdraw an LoA for a particular applicant should advise the MF Administration Unit of the reasons for doing so. Submit a cover letter (in proper non-eCTD or eCTD format through the CESG. You may list multiple applicants whose access is being withdrawn in a single cover letter.

Do not include withdrawal of access letters in Module 1.2.6. Authorization for Sharing Information.

For MFs in the eCTD format, the attribute "Delete" must be applied to letters of access for applicants whose access is being withdrawn. This should be done in Module 1.2.6 Authorization for Sharing Information.

The MF holder should inform the applicant whose LoA is being withdrawn from the MF of the withdrawal. The letter should clearly state the date after which the material will no longer be supplied to the applicant. Substances supplied before the date where the LoA was withdrawn due to the termination of a supply agreement may still be used in authorized products, according to the conditions of authorization. However, the MF may no longer be referenced in subsequent applications.

Do not provide Health Canada with copies of correspondence they give to applicants regarding withdrawal of access.

Health Canada will keep the withdrawn LoA according to appropriate procedures established for record retention and disposal, in accordance with the *Library and Archives of Canada Act*. When an LoA is withdrawn, the previously manufactured drug substance or material will no longer be supplied to the applicant.

2.6 Master File Closures

MF holders who wish to close an MF should notify the MF Administration Unit in writing. The cover letter should:

- be in the proper non-eCTD or eCTD format and submitted through the Common Electronics Submission Gateway (CESG)
- indicate the reason for the closure
- include a statement that their obligations have been fulfilled
    - synthesis, manufacturing process and quality controls have been kept up-to-date
    - changes that affected applicants have been communicated to each of them and to Health Canada

On closure, MF holders should provide a list of all applicants using the MF to Health Canada.

When an MF is closed, the product referred to in the MF can no longer be manufactured for use in Canadian marketed drug products. As well, the MF may no longer be referenced in subsequent Canadian drug submissions, DIN applications or CTAs unless the CBI is submitted directly to the applicant who will include the information in their drug submission, DIN application or CTA.

Active pharmaceutical ingredients (APIs) manufactured and tested in accordance with the registered procedures and manufactured and shipped to the drug product manufacturer before an MF is closed can be used in Canadian marketed drug products until the stockpile is depleted or the API has expired, whichever comes first. Complete records for the shipment should be maintained in accordance with Canadian GMPs.

Health Canada will assess the reasons for the closure and start post-market activities, if necessary. If the reasons for closing the MF are related to safety, the MF holder should:

- inform the applicant of those reasons and
- contact Health Canada on the health risk assessment and any recall actions taken

Health Canada will retain the MF following appropriate procedures established for record retention and disposal in accordance with the *Library and Archives of Canada Act*. We may access the MF after the file is closed in accordance with the law.

Health Canada will close and archive an MF that we have:

- not accessed
- assessed in support of a drug submission, DIN application or CTA within 5 years following the initial registration

MF holders who wish to reactivate the MF with Health Canada should:

- file the MF in the non-eCTD format or eCTD format through the Common Electronic Submissions Gateway (CESG)
- state in a cover letter their wish to reactivate the MF
- provide updates and applicable data since the date of the MF closure

The same MF number and dossier ID will be retained and fees for a new MF registration will be applied.

For more information on filing requirements for MF reactivations, refer to the section on format and structure of the master file.

3. Contact Us

Questions or comments about this guidance document and the MF process:

Master File Administration Unit
Office of Submissions and Intellectual Property
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada
Email: dmf.enquiries-fmm@hc-sc.gc.ca

Pharmaceutical Drugs
Bureau of Pharmaceutical Sciences (BPS) Pharmaceutical Drugs Directorate
Health Products and Food Branch
Health Canada
Email: bpsenquiries@hc-sc.gc.ca

Office of Clinical Trials
Therapeutic Products Directorate
Health Products and Food Branch
Health Canada
Address Locator: 3105A
Ottawa ON K1A 0K9
Email: oct.enquiries-requetes.bec@hc-sc.gc.ca

Biologic and Radiopharmaceutical Drugs
Office of Regulatory Affairs
Biologic and Radiopharmaceutical Drugs Directorate
Health Canada
100 Eglantine Dr
Address Locator: 0601C
Ottawa ON K1A 0K9
Email: brdd.ora@hc-sc.gc.ca

4. References

4.1 Health Canada Documents

Legislation:

- Food and Drugs Act
- Food and Drug Regulations
- Medical Devices Regulations
- Access to Information Act
- Library and Archives of Canada Act

Related guidance documents:

- Master File application form
- Guidance for industry: The management of drug submissions and applications
- Guidance document on post-drug identification number (DIN) changes
- Guidance document: Preparation of drug regulatory activities in the non-eCTD format
- Guidance document: Preparation of regulatory activities in the electronic common technical document (eCTD) format (available upon request from the "Filing submissions electronically" page)
- Guidance for industry: Preparation of veterinary new drug submissions
- Draft guidance document - Quality (chemistry and manufacturing) guidance: New drug submissions (NDSs) and abbreviated new drug submissions (ANDSs)
- Evidence for quality of finished natural health products
- Post-notice of compliance (NOC) changes: Quality document
- Notice: Guidance for industry: Pharmaceutical quality of aqueous solutions
- Guidance for industry: Pharmaceutical quality of inhalation and nasal products
- Guidance document: Quality (chemistry and manufacturing) guidance: Clinical trial applications (CTAs) for pharmaceuticals
- Guidance document for clinical trial sponsors: Clinical trial applications
- Guidance for industry: Stereochemical issues in chiral drug development
- Guidance for industry: Preparation of quality information for drug submissions in the CTD format: Biotechnological/biological (biotech) products
- Preparation of the quality information for drug submissions in the CTD format: Blood products
- Preparation of the quality information for drug submissions in the CTD format: Conventional biotherapeutic products
- Guidance document: Harmonized requirements for the licensing of vaccines and guidelines for the preparation of an application
- Guidance document: Submission and information requirements for extraordinary use new drugs (EUNDs)
- Good manufacturing practices guide for drug products (GUI-001)
- Summary of Annex 3B to the Good manufacturing practices guide: Positron-emitting radiopharmaceuticals
- Cleaning validation guide (GUI-0028): Summary

- Process validation: Aseptic processes for pharmaceuticals
- Guide to validation: Drugs and supporting activities (GUI-0029)
- Guidance document: Preparation of clinical trial applications for use of cell therapy products in humans
- Guidance document: Plant molecular farming (PMF) applications: Plant-derived biologic drugs for human use

4.2 International Council on Harmonisation Guidelines

- Q1A(R2): Stability testing of new drug substances and products
- Q1B: Stability testing: Photostability testing of new drug substances and products
- Q1C: Stability testing requirements for new dosage forms
- Q1D: Bracketing and matrixing designs for stability testing of drug substances and drug products
- Q1E: Evaluation of stability data
- Q2(R1): Validation of analytical procedures: Text and methodology
- Q3A(R): Impurities in new drug substances
- Q3B(R): Impurities in new drug products
- Q3C(R8): Impurities: Guideline for residual solvents
- Q3D(R1): Guideline for elemental impurities
- Q5A(R1): Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin
- Q5B: Analysis of the expression construct in cells used for production of r-DNA derived protein products
- Q5C: Stability testing of biotechnological/biological products
- Q5D: Derivation and characterisation of cell substrates used for production of biotechnological/biological products
- Q5E: Comparability of biotechnological/biological products subject to changes in their manufacturing process
- Q6A: Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances
- Q6B: Specifications: Test procedures and acceptance criteria for biotechnological/biological products
- Q7: Good manufacturing practices guide for active pharmaceutical ingredients
- Q7 Q&As: Questions and answers: Good manufacturing practice guide for active pharmaceutical ingredients
- Q8(R2): Pharmaceutical development
- Q9: Quality risk management
- Q10: Pharmaceutical quality system
- Q11: Development and manufacture of drug substances (chemical entities and biotechnological/biological entities)
- ICH Q11 Questions and answers: Selection and justification of starting materials for the manufacture of drug substances

4.3 International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Documents

- GL3(R): Stability testing of new veterinary drug substances and medicinal products
- GL4: Stability testing: Requirements for new dosage forms
- GL5: Stability testing: Photostability testing of new drug substances and products
- GL8: Stability testing for medicated premixes
- GL10(R): Impurities in new veterinary drug substances
- GL11(R): Impurities in new veterinary medicinal products
- GL17: Stability testing of new biotechnological/biological veterinary medicinal products
- GL18: Impurities: Residual solvents in new veterinary medicinal products, active substances and excipients
- GL39: Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: Chemical substances + decision trees
- GL40: Test procedures and acceptance criteria for new biotechnological/biological veterinary medicinal products
- GL45: Bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products

5. Sample Letter Templates

Appendix 1: Letter of Access Sample

(Date)

Master File Administration Unit
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada

Dear Sir or Madam:

Re: Letter of Access - (Master File Name) MF # (YYYY-XXX) (or New Master File if a New Submission)

Please accept this letter as authorization for Health Canada to review (Master File Name, MF # YYYY-XXX) referenced by:

Applicant/Sponsor Name Street Address, State/Province, Country Postal Code

In support of their drug submissions, DIN applications or clinical trial applications filed with the Pharmaceutical Drugs Directorate or the Biologic and Radiopharmaceutical Drugs Directorate of the Health Products and Food Branch.

Yours sincerely,

(Signature)

Note: Please do not include any reference to submission type/number or product lines/names in your letter of access. For CTAs, you may also include the name of the sponsor of the CTA, name of the CTA and protocol number.

Appendix 2: MF Agent or Third-Party Authorization Letter Sample

(Date)

Master File Administration Unit
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada

Dear Sir or Madam:

Re: Master File Agent Authorization/Authorization for a Third Party Filing on Behalf of (MF Holder Company Name) - (Master File Name) MF # (YYYY-XXX)

Please be advised that we have appointed (company name/name) to be our authorized master file agent/act as a third party Filing on our behalf for the Canadian market. (Company name/name) will be responsible for:

a) filing MF related transactions
b) handling deficiencies
c) managing the payment of fees
d) managing associated correspondence and
e) filing updates and administrative changes

Yours sincerely,

(Signature)

Appendix 3: CEP Attestation Letter Sample

(Date)

Master File Administration Unit
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada

Dear Sir or Madam:

Re: Drug Substance - CEP # XXXXXXXXXXXXX

On behalf of [API manufacturer name/MF holder], I attest to the following:

1. I authorize Health Canada to refer to the CEP along with Report A and the specifications authorized by EDQM.
2. I attest that [API manufacturer name/MF holder] will provide Health Canada with a copy of the entire EDQM dossier and associated correspondence in electronic form on request from Health Canada.
3. I attest that GMP for APIs will be applied commencing with the starting material authorized by EDQM.
4. I attest that there have been no significant changes in the manufacturing method and controls following the granting of the CEP, or its last revision, by EDQM.
5. I attest that any conditions/additional tests attached to the CEP by the EDQM and any tests and limits additional to those in the Ph. Eur. monograph required for the intended use of the substance will be applied to each batch of the drug substance destined for the Canadian market.
6. I attest that the in-house method [insert reference to in-house method(s) not mentioned on the CEP has/have] been submitted to the EDQM and are used as described in the dossier submitted to EDQM.
7. I attest that the API that will be produced for the Canadian market will be manufactured in a manner using a manufacturing process that is identical to the route evaluated by the EDQM. In addition, any in-process tests or tests of intermediates submitted to or requested by EDQM will be applied in the manufacture of the API destined for the Canadian market.
8. I attest that the specifications provided to the applicant reflect the final set of API specifications and the in-house method(s) listed on the specifications which were submitted to and assessed by the EDQM.

Yours sincerely,

[Authorized representative name]
[Position title]
[API manufacturer name]

Appendix 4: BSE/TSE Declaration Sample

(Date)

Master File Administration Unit
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada

Dear Sir or Madam:

Re: BSE/TSE Declaration for MF NAME, MF # YYYY-XXX (dossier ID: e/f#########)

We [MF holder's name] declare that product(s) manufactured at the facilities/sites listed in the above-referenced master file is/are not manufactured using any materials of animal origin that are susceptible to BSE/TSE contamination.

OR

We [MF holder's name] declare that product(s) manufactured at the facilities/sites listed in the above-referenced master file is/are manufactured using any materials of animal origin that are not susceptible to BSE/TSE contamination.

OR

We [MF holder's name] declare that product(s) manufactured at the facilities/sites listed in the above referenced master file is/are manufactured using materials of animal origin (either as starting material, reagent or processing aid) that are susceptible to TSE/BSE contamination.

Complete data on the risk of transmitting BSE/TSE has been provided in Section 3.2.S.2.3 Control of Materials or 3.2.P.4.5 Excipients of Human or Animal Origin of the application.

AND

We [MF holder's name] declare that product(s) manufactured at the facilities/sites listed in the above-referenced master file are/are not susceptible to BSE/TSE contamination. (Type V)

Yours sincerely,

[MF contact person/authorized representative name]
[Position title]

Note: The statements outlined above are separated by the word "OR". MF holder should declare the BSE/TSE risk by choosing the statement as appropriate.

Appendix 5: Statement of Commitment Sample

(Date)

Master File Administration Unit
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada

Dear Sir or Madam:

Re: Statement of Commitment for MF name, MF # YYYY-XXX (dossier ID: e/f########)

We, [MF holder's name], certify that, to the best of our knowledge and belief, with reference to the application pertaining to [API NAME/MF NAME] manufactured in our plant at [LOCATION]:

1. All the information and material included in the application and solicited information are accurate and complete, and that the summary documents correctly represent the information and material referred to in the application. No information is false or misleading and no omissions have been made that may affect its accuracy and completeness.
2. The product is manufactured in accordance with the process described herein and each lot of the product released will conform to the specifications if tested by the methods described in the MF.

   In addition, we agree to maintain the MF in order to keep the file open and active by updating the information contained in this document by submitting an "Update the MF" when significant changes to the MF should be submitted according to applicable guidance documents on post-NOC changes are made.

   Yours sincerely,

   [MF contact person/authorized representative name]
   [Position title]
   [MF holder name]