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Guidance Document

Master Files (MFs) - Procedures and Administrative Requirements

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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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Date	January 2, 2019	Date	May 1, 2017

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.

Foreword

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

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

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

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

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1. Introduction

A Master File (MF) is a reference that provides information about specific processes or components used in the manufacturing, processing, or packaging of 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 to the sponsors of a drug submission, DIN (Drug Identification Number) application or clinical trial application (CTA) (hereafter referred to as the Applicants). 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 IV MFs, and outlines the registration requirements for new MFs as well as other MFs transactions including administrative changes, updates, withdrawals and closures.

1.1 Policy objective

To provide direction on the procedures that allow MF Holders or authorized MF Agents to file CBI directly with Health Canada to be referenced in support of an Applicant's drug submission (including DIN applications) or CTA with respect to quality information.

1.2 Policy statements

For the purpose of this guidance document and in accordance with the Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document (eCTD) Format, MFs are categorized as regulatory transactions (refer to Section 1.4 for definition).

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

It is the responsibility of the Applicants to submit non-confidential business information provided by the MF Holder or authorized MF Agent, obtained in the public domain, and/or developed by the Applicant in the drug submission, DIN application or CTA.

The Applicant should ensure that the information included in the MF is up-to-date and that the MF has been received by Health Canada by contacting the MF Holder or authorized MF Agent for confirmation before filing their submission, DIN application or CTA to Health Canada.

The Restricted Part of MF will be held in strict confidence and will be used in support of the drug submission or CTA only upon receipt of a written letter of access (LoA) from the MF Holder or authorized MF Agent.

The LoA is signed by the MF Holder or authorized MF Agent and 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.

1.3 Scope and application

This guidance document applies to all MF Holders, authorized MF Agents or Applicants using an MF to support drug submissions and DIN applications for human use or CTAs; and, Health Canada employees involved in MF processes. Submissions and applications include: an Extraordinary Use New Drug Submission (EUNDS), New Drug Submission (NDS), 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 one Applicant.

The guidance document also applies to MF Holders or authorized MF Agents intending to file MFs that are cross-referenced in drug submissions and DIN applications for both human and veterinary use or CTAs. For information on the requirements for MFs related to veterinary drug products and substances, refer to the Guidance for Industry Preparation of Veterinary New Drug submissions.

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, refer to the Product Licence Application form or contact the Natural and Non-prescription Health Products Directorate (NNHPD).

MFs are classified according to the following types:

Table 1: Master File Classifications

Type I Active Substance Master Files (ASMFs)	Type II Container Closure System Master Files (CCS MFs)	Type III Excipient Master Files (Excipient MFs)	Type IV Dosage Form Master Files (Dosage Form MFs)
<p>For pharmaceuticals: Active Pharmaceutical Ingredients (API) (drug substances), starting materials or intermediates used in the manufacture of a drug substance.</p> <p>For biologics: Drug substances can include bulk process intermediates, vaccine antigens, adjuvants (except for alum), albumin (except when</p>	<p>Container closure systems (CCS) or CCS components.</p>	<p>All excipients including excipients of biological origin (e.g., albumin), capsule shells, coating ingredients, colourants, flavours, and other additives (e.g., gelatin, alum and growth media).</p>	<p>Dosage forms and drug product intermediates.</p>

used as an excipient), critical raw materials for radiopharmaceuticals or vectors for gene therapy.			
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1.4 Definitions¹

Active Pharmaceutical Ingredient (API)

See 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 (see Section 2.1).

Authorized MF Agent

Any person appointed by the MF Holder to file an MF or serve on behalf of the MF Holder.

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 which may transmit the Bovine/Transmissible Spongiform Encephalopathies (BSE/TSE) and that the risk of transmitting agents of animal spongiform encephalopathies has been minimized.

Please refer to the Master File (MF) Application Form for Human and Veterinary Drugs and Clinical Trial Applications (CTAs).

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 package provided to Health Canada.

Dosage Form

A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Dosage Form Manufacturer

The company which 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 in the manufacture of 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 or Authorized MF Agent indicating 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 who submitted the MF. This may be the manufacturer of the product described in the MF and/or the originator of the CBI.

MF Update

An update is a revision or change to any information provided in an existing MF and/or replacement for an existing MF.

Regulatory Activity

a collection of all regulatory transactions throughout the process of a specific activity which includes, but is not limited to, an NDS, ANDS, DIN Application, CTA and 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 (see Section 2.1).

Statement of Commitment

A declaration from the MF Holder or authorized MF Agent that the information provided in the MF is true and accurate.

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) which was created to promote collaboration and convergence in generic drug regulatory programs. This guidance document also incorporates procedures and terminology resulting from the adoption of International Council for Harmonisation (ICH)

guidelines and the use of Certificates of Suitability to the Monographs of the European Pharmacopeia (CEPs). For the purpose of this document, and in keeping with international best practices, the term Master File (MF) is used (previously known as Drug Master File (DMF)).

2. Guidance for implementation

2.1 Health Canada Master Files

An MF is submitted by the MF Holder or authorized MF Agent only in cases where the company does not wish to disclose CBI to the Applicant of the drug submission, DIN application or CTA.

Type I and Type IV MFs are divided in two parts: the “Applicant’s Part” and the “Restricted Part”. The Restricted Part contains the information that the MF Holder regards as confidential and is filed by the MF Holder or authorized MF Agent to Health Canada directly. The Applicant’s Part contains the information that the MF Holder regards as non-confidential. It is provided to the Applicant and is usually included as part of the Applicant’s drug submission, DIN application or CTA, with the accompanying LoA. The LoA is signed by the MF Holder or authorized MF Agent and 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 or CTA.

2.1.1 Confidentiality

Within Health Canada, the Restricted Part of the MF is kept confidential and officials of Health Canada 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 that protects third party information such as trade secrets; confidential financial, commercial, scientific or technical information; information the disclosure of which could reasonably cause financial loss or gain or prejudice to the competitive position of a third party; or 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 that the product may present a serious risk of injury to human health. Section 21.1(3) of the Food and Drugs 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 protection or promotion of human health or the safety of the public. Refer to Health Canada’s Draft Guidance Document - Disclosure of Confidential Business Information under Paragraph 21.1(3)(c) of the Food and Drugs Act.

2.1.2 Registration Requirements

It is recommended that MFs are filed no more than one year but no less than 2 months prior to the filing of a drug submission, DIN application or CTA making reference to those MFs. All MFs are expected to include at least one LoA at the time of filing.

For New MF Registrations the following electronic documents should be included²:

- One signed cover letter, stating the MF name

- MF Agent Authorization Letter from MF Holder, if applicable (see Section 2.1.9 and Appendix 3)
- MF Application Form
- MF Application Fee Form and appropriate fees
- CEP and Attestations (for Type I MFs only), if applicable (see Appendix 4), and
- LoAs (see Section 2.1.7 and Appendix 2)

Type I and Type IV MFs should include the following:

- Applicant and the Restricted Parts
- A copy of a Quality Overall Summary (QOS) in Microsoft Word format
- The Certified Product Information Document (CPID) in Microsoft Word format. 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 that the components are similar (e.g., a complete container closure system, different stopper formulations, multiple flavours). A limit of 50 components will be enforced per 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 QOS in lieu of the Applicant's Part and Restricted Part. In addition, 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 in conjunction with an Applicant's drug submission, DIN application or CTA for which an LoA was provided. Health Canada does not authorise the MF except in conjunction with a DIN, Notice of Compliance (NOC) or No Objection Letter (NOL) issued for the associated drug product. As such, Health Canada does not have a database that is accessible to the public listing all MFs registered in Canada.

2.1.3 Naming a Master File

For Type I MFs, the preferred name of the MF should be the generic name (e.g., the International Non-proprietary Name (INN) for an active pharmaceutical ingredient) 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.

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 Section 2.1.10 When to File a New MF Registration. Type II and Type III MFs may contain information on different products within a family of products (e.g., for stoppers manufactured using the same formulation). Type IV MFs may have more than one product strength with the same formulation except for changes necessary to accommodate the different strengths. However in such cases, the information for each product should be clearly differentiated within the Type IV MF.

If the MF Holder has more than one MF for a similar product, the cover letter should state this explicitly and provide information to distinguish the different products. Information distinguishing the different products should be provided in a side-by-side comparison table. The MF Holder should provide a name that distinguishes the MF from any previously registered MFs.

2.1.4 Format and structure of the Master File

As of January 1, 2016, Health Canada no longer accepts paper copies of MFs. MFs must follow the filing and formatting requirements outlined in the Guidance Document Preparation of Drug Regulatory Activities in the “Non-eCTD Electronic-Only” Format (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html>) which includes guidance on MF structure and content, as well as the breakdown of the MF’s Applicant and Restricted Parts. Also refer to the 2015 Notice - Re: Preparation of Drug Master File (DMF) in "Non-eCTD Electronic-Only" Format (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/notice-preparation-drug-master-file-non-ectd-electronic-only-format.html>) for additional information on electronic filing of MFs.

MF Holders or authorized MF Agents may also file their MFs in eCTD format and should consult the Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document Format (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/ectd/preparation-drug-submissions-electronic-common-technical-document.html>). Prior to filing an eCTD MF, MF Holders or authorized MF Agents should contact Health Canada via email to hc.ereview.sc@canada.ca.

All documents should be provided in Portable Document Format (PDF) or in Microsoft Word format. Documents may also be provided in Microsoft Excel format where applicable.

As of March 2016, all paper MFs previously registered with Health Canada must have been converted to a non-eCTD or eCTD electronic format. Any MFs that have not been converted into a non-eCTD or eCTD electronic format are considered to be suspended (no further access to the MF for assessment will be granted and no updates will be accepted). If the MF Holder wishes to reactivate a suspended or closed MF in the future, a cover letter should be sent to Health Canada with the converted MF in electronic 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.

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 the entire MF in their first eCTD transaction. It is not sufficient to convert the MF into the eCTD format by simply submitting the next transaction in eCTD via the Common Electronic Submission Gateway (CESG) (i.e., submitting an LOA or update in eCTD format as a subsequent transaction for an MF currently in non-eCTD format).

Please note: once an MF has been filed in or converted into the eCTD format, all subsequent transactions must also be filed in the eCTD format via the CESG. Any subsequent transactions filed in the non-eCTD format for MFs already filed in eCTD format will be rejected and shredded or returned to the sender at their expense.

2.1.5 Official language of correspondence

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

2.1.6 Where to send Master File registrations

MF transactions in non-eCTD format should be filed to the MF Administration Unit:

Master File Administration Unit
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada
Finance Building, 2nd Floor
Address Locator: 0201A
101 promenade Tunney's Pasture Driveway
Ottawa, Ontario
K1A 0K9

Email: hc.dmf.enquiries-fmm.sc@canada.ca

Fax number: 613-941-0825

MF transactions in eCTD format must be submitted via the CESG.

A completed and signed MF Application Form must accompany the MF.

2.1.6.1 Shipping/customs information

MF Holders or authorized MF Agents are responsible for all costs associated with shipping documents and electronic information to Health Canada, including any applicable customs and/or brokerage fees. Packages must indicate "Terms DDP (Delivered Duty Paid)". Any packages filed to Health Canada with a request for additional charges by a shipper or brokerage firm will be returned to the sender at their expense.

2.1.7 Letters of Access (LoA)

MF Holders or authorized MF Agents file 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. CBI will only be used for the purpose of the assessment of the Applicant's drug submission, DIN application or CTA if the MF Holder or authorized MF Agent provides an LoA on official company letter head signed by the MF Holder or Authorized MF Agent (see Appendix 2). All LoAs remain valid throughout the life-cycle of an MF.

2.1.7.1 Information to include in the Letter of Access

The following information should be included in the LoA:

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

The following information should NOT be included in the LoA:

- Product name or line
- Submission type or number

Please refer to Appendix 2 for a sample letter of access.

2.1.7.2 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, an MF application fee form and is subject to the applicable fees. The LoA must be 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, and to the Applicant prior to filing their drug submission, DIN application or CTA. LoAs provided to the applicant must be identical 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 result in delays in the assessment of the drug submission, DIN application or CTA.

For Type I and IV MFs, an LoA grants access to an MF in its entirety. The LoA is valid for all products and submissions from the Applicant cross-referencing the MF. Therefore, only one 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 one LoA is required per Applicant for the duration of the MF's lifetime. When granting access for an additional component, 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 are required to file an LoA granting another MF Holder access to their MF. 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 to the Type IV MF.

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) remain valid. No fees will be applied for an MF Holder name change where no new LoAs are issued. Please refer to Section 2.1.11 for more information on MF fees.

Please contact the MF Administration Unit prior to re-filing an LoA to confirm requirements (see Section 2.1.6).

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. Refer to Section 2.1.8 for information on submitting CEPs.

2.1.7.3 Letters of Access for clinical trials (pharmaceuticals and biologics)

LoAs can be filed in support of all phases or for only specified phases of a CTA. This is at the discretion of the MF Holder.

The LoA should name the sponsor of the CTA and the name of the Clinical Trial. Additional information such as hospital information, principal investigator and protocol number can be provided.

The LoA should be filed directly to the MF Administration Unit with accompanying MF Application Fee Form and fee. A copy should be included in the CTA, CTA-N or CTA-A. No additional copy should be provided outside of the Applications.

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

At the time of filing of a Type I MF, MF Holders or authorized MF Agents are encouraged to include the CEP (as applicable) or confirm that no CEP is available. If a CEP is not available at the time of filing of the MF, it should be provided as soon as the CEP becomes available. In this case, no fees will be applied.

If the MF is revised/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.

All CEPs should be sent to the MF Administration Unit with the relevant attestations as outlined in Appendix 4. When providing a revised CEP, new attestations should be provided. The CEP number should be stated in the attestations. Please see Appendix 4 for a sample CEP Attestation.

A CEP can be submitted as supporting information for an MF when the MF is not completely identical to the CEP dossier. Provision of a CEP is recommended as even if the MF is different from the dossier submitted to EDQM (e.g. USP standard is declared), the provision of the 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. If differences between the MF and the CEP dossier exist, these differences should be clearly declared and a side-by-side comparison table of the MF and CEP provided.

Please note that CEPs can also be provided directly in the Applicant's drug submission or DIN Application in lieu of providing ASMFs. Please see the Guidance Document: Use of Certificates of Suitability as supporting information in Drug Submissions (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-document-use-certificates-suitability-supporting-information-drug-submissions.html>) for further information on how to use this alternate procedure.

2.1.9 Appointment of the authorized Master File agent

When an Agent is appointed by the MF Holder (see Appendix 3) they are responsible for all correspondence related to the MF, including but not limited to the following:

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

When the MF Holder is not based in North America, it is recommended that an agent be located in North America in order to expedite communications. Once appointed, an authorized MF Agent may perform all functions listed in this guidance document on behalf of the MF Holder.

2.1.10 When to file a new Master File registration

When two (or more) MFs are being filed for similar active substances and differ only due to additional processing steps or minor variations, cross-references to the other related MFs can be included in the cover letters to expedite the assessment of the common information. A side-by-side comparison table (in Module 1, Section 1.0.7 General Note to Reviewer) should also be included.

In some cases, a new Type I MF registration is required. The examples below 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 substantially different route of synthesis (i.e. resulting in a different specification for the active substance)
- different polymorphic forms (resulting in substantially different physicochemical and/or pharmacokinetic properties)
- any other change to the active substance that results in substantially 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 is a substantial change in the safety of the active substance)

The following examples will not necessarily be considered to represent a new Type I MF and in most cases could be incorporated in a single MF with the same MF number.

- slightly different routes of synthesis which do not result in substantially different physicochemical and/or pharmacokinetic properties
- different manufacturing sites using the same or similar routes of synthesis (i.e. same specification for the active substance)
- different particle size grades (this 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 which do not result in substantially different physicochemical and/or pharmacokinetic properties

MF Holders or authorized MF Agents should consult the relevant programme area before submitting the MF if they are unsure of whether a separate MF should be submitted (see Appendix 1).

2.1.11 Master File fees

As the MF process is voluntary and represents solely a private benefit, the non-regulatory charges are fully cost recovered under the Ministerial Authority to Enter into Contract and have been developed in accordance with Health Canada's External Charging Policy and Guidelines and relevant Treasury Board of Canada Secretariat (TBS) policies (e.g., Policy on Service Standards for External Fees).

Fees are collected for the registration and processing of each new MF, LoA and update. If an LoA is re-filed then the fee is applicable each time it is re-filed.

Refer to the MF Application Fee Form regarding fees for the processing of new MFs, LoAs and updates.

Fees are increased annually by 2% on the first of April each year. For further information on how to pay fees for MFs, refer to the Guidance Document: How to Pay Fees to Health Products and Food Branch (HPFB) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/cost-recovery/pay-fees.html>).

MFs are not eligible for fee mitigation.

2.2 Processing of Master Files

When an MF registration package is received the following activities are performed:

- assigning an MF number and a dossier ID* to the MF (only for New MF registrations), and
- verifying that the correct information, documents and forms have been filed in the correct format (refer to Section 2.1.4 Format and Structure of the MF) and that all submitted information, documents and forms are complete for administrative purposes (including those related to cost-recovery)

*For MFs submitted in eCTD, the dossier ID is assigned before the submission package is received.

Once the MF registration package is administratively complete**:

- a filing date is assigned (which is the date when the MF is considered administratively complete), and
- an acknowledgement letter (with an MF number and dossier ID) is sent to the designated MF contact person (MF Holder or authorized MF Agent) as listed on the MF Application Form

If the required information, forms or fees are missing, incomplete, or are provided in the incorrect format, the MF will be placed on Administrative Hold, in which case the MF Administration Unit will issue an administrative process hold letter to the MF contact person requesting the missing information.

** A file is considered administratively complete when all processing and cost recovery requirements are met. All required information, forms and correct fees are provided in the correct format and are complete.

2.2.1 Administrative holds

At different stages during the administrative processing of MFs it may be necessary to place the MF transaction on Administrative Hold when the MF package is incomplete (i.e., missing required information, forms or fees). This hold will remain in place until the required information is submitted in the appropriate format.

There are two categories of Administrative Holds:

A. Process Hold

The MF Administration Unit will place the MF on Process Hold when the MF is considered administratively incomplete, or when the information is filed as the wrong transaction type (i.e., new MF should have been filed as an update). Failure to respond to a request for additional or corrected information in the prescribed time will result in the transaction not being processed. When the reason for the Process Hold is addressed, the MF transaction is considered administratively complete and a filing date will be applied.

B. Cost Recovery Hold

In the event that the MF Application Fee Form or applicable fee is not provided or the applicable fee is insufficient, the MF Administration Unit will request the fee form and payment from the MF contact person. Pending receipt of the fee form or payment, the transaction will be placed on a Cost Recovery Hold. If the fee form or payment is not received in the timeframe indicated in the letter, the transaction will not be accepted. Failure to respond to a request for additional or corrected information in the prescribed time will result in the transaction being shredded. When the reason for the Cost Recovery Hold is addressed, the MF transaction is considered administratively complete and a filing date will be applied.

2.2.2 Application and File Maintenance requirements

All correspondence (e.g., cover letters or LoAs to an MF) should come from the MF Holder or authorized MF Agent, where applicable. Any information filed by a third party will be rejected and shredded.

All information that is included in the Applicant's Part of the MF must be provided to the Applicant of the drug submission, DIN application or CTA referencing the MF, and is to be included in their submission or applications to Health Canada.

2.2.3 Master File performance standards

All information and material filed with an MF transaction will be processed by the MF Administration Unit within 30 calendar days of receiving a complete package (i.e., the date the MF is considered administratively complete).

2.3 Assessment of Master Files

MFs are always assessed in conjunction with a drug submission, DIN application or CTA and therefore, decisions rendered on the quality-related data in an MF pertain to the drug seeking market authorization or clinical trial authorization.

Note that the requirements of Division 2 - Good Manufacturing Practices (GMP) of the Food and Drug Regulations apply to all buildings fabricating, packaging/labelling, testing APIs and dosage forms. For additional information please consult Division 1A and 2 of the Regulations and applicable guidance.

For specific information on the technical requirements of an MF, the following guidance documents should be consulted:

For pharmaceuticals

- Guidance Document - Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-document-quality-chemistry-manufacturing-guidance-new-drug-submissions-ndss-abbreviated-new-drug-submissions.html>)
- Guidance Document: Addendum - Quality (Chemistry and Manufacturing) Guidance: Questions and Answers (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-document-addendum-quality-chemistry-manufacturing-guidance-questions-answers.html>)
- Guidance Document - Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/quality-chemistry-manufacturing-guidance-clinical-trial-applications-pharmaceuticals.html>)
- Certified Product Information Document - Chemical Entities CPID-CE (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/templates/certified-product-information-document-chemical-entities-cpid-applications-submissions-drug-products.html>)

For biologics

- Preparation of the Quality Information for Drug Submissions in the CTD Format: Biotechnological/ Biological (Biotech) Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/guidance-industry-biotechnological-biological-biotech-products.html>)
- Preparation of the Quality Information for Drug Submissions in the CTD Format: Blood Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/guidance-industry-conventional-biotherapeutic-products.html>)

- Preparation of the Quality Information for Drug Submissions in the CTD Format: Conventional Biotherapeutic Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/guidance-industry-conventional-biotherapeutic-products.html>)
- Guidance Document Harmonized Requirements for the Licensing of Vaccines and Guidelines for the Preparation of an Application (https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/drugs-drogues/ctd_vaccin-eng.pdf)
- Blank Certified Product Information Document (Schedule D Drugs) (CPID (Schedule D Drugs)) Template in the CTD Format (<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/certified-product-information-document-template-format.html>)
- Draft Guidance for Industry, 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 (<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/draft-guidance-industry-preparation-quality-information-radiopharmaceuticals.html>)

For specific information on the content of Type II and Type III MFs not covered in the above guidance documents, the relevant programme area should be contacted (see Appendix 1).

2.3.1 Solicited Information

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

All communications with respect to 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 or authorized MF Agent and Health Canada officials. If any comments are considered necessary concerning the Restricted Part of the MF, they will be forwarded directly to the MF Holder in the form of an MF Letter of Deficiency or a clarification request. Comments pertaining to the Applicant's Part of the MF (e.g., analytical methods, stability data) may also be forwarded to the MF Holder.

When deficiencies are noted within the MF's Restricted Part, the Applicant will be notified that there are outstanding issues that need to be addressed before the MF can be considered acceptable to support their 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. No new Letter of Deficiency will be issued to the MF Holder or authorized MF Agent unless new comments need to be forwarded (e.g., different requirements for API 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 further clarification of information is required, a 15 calendar day clarification request will be issued to the MF Holder by email or fax. If the MF Holder does not respond to a clarification request within the given timeframe, or if the MF has a significant number of deficiencies, then a Letter of Deficiency will be issued.

The MF Holder will be required to respond to the Letter of Deficiency within the timeframe specified in the Letter. If additional time is required, the MF Holder should contact the Applicant for the associated submission who will contact the Director of the relevant assessment bureau to request an extension.

If the response to a Letter of Deficiency has yet to be received or is not satisfactory at the time the decision is being taken on the Applicant's drug submission, then a Notice of Non-Compliance (NON) will be issued to the Applicant. No additional correspondence will be sent to the MF Holder however, they are expected to respond within the timeframe given to the Applicant to respond to the NON.

2.3.2.1 Clarifications requests during Master File assessment in support of a Clinical Trial Application

If further information is required during the assessment of an MF in support of a CTA, a 2 calendar day clarification request will be issued to the MF Holder or authorized MF Agent, and the Applicant will be notified in writing. The Applicant should ensure a timely response is sent by the MF Holder or authorized MF Agent. Failure to provide a satisfactory response within the specified time frame could result in withdrawal of the CTA or issuance of a Not Satisfactory Notice as per the Guidance Document: For Clinical Trial Sponsor: Clinical Trial Applications (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html>).

2.3.3 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 as per the Guidance Document Preparation of Drug Regulatory Activities in the "Non-eCTD Electronic-Only" Format³. Any responses to clarification requests or responses to Letters of Deficiency received in the incorrect format will be put on administrative process hold until the response is received in the correct non-eCTD format. For MFs filed in eCTD format, responses must be submitted as a new sequence through the CESG.

2.3.4 Master File assessment reports

MF Assessment reports will be sent with Letters of Deficiency. Upon completion of the MF Assessment, reports may be requested from the Office of Planning, Performance and Review Services by MF Holders or authorized MF Agents.

Office of Planning, Performance and Review Services (OPPRS)
Therapeutic Products Directorate
Health Products and Food Branch
Address Locator: 3002C
Health Canada
Ottawa, Ontario
K1A 0K9

E-mail: hc.opprs.enquiries-enquetes.bprse.sc@canada.ca
Telephone: 613-941-1248
Fax: 613-957-1483

2.4 Updates to a registered Master File

Updates are to be filed by the MF Holder or Authorized MF Agent and should be addressed to the MF Administration Unit (see Section 2.1.6).

Updates to the MF are not required on a timed basis, but are required when changes are in accordance with the reporting categories outlined in Health Canada's Guidance Document on Post-Drug Identification Number (DIN) Changes (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-drug-identification-number-changes.html>), Post-Notice of Compliance (NOC) Changes - Quality Guidance Document (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/quality-document.html>) or Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html>). All updates are subject to fees and should be accompanied by the MF Application Fee Form and appropriate fees.

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 or IV)

Additional administrative documents include:

- A summary of changes (side by side comparison) of the affected sections of the MF listing the level of the change and the impact of that change (in Module 1, Section 1.0.7 General Note to Reviewer).
- An up-to-date list of all Applicants authorized to access the MF.
- A revised MF Application Form.
- MF Application Fee Form and fees.

All affected data should be included in Module 3.

When filing an update to Type II and Type III MFs for an additional formulation or component, a limit of 50 components/formulations per MF will be enforced. Additional components or formulations should be filed in a new MF. The MF Holder or authorized MF Agent should include a current numbered index listing all components/formulations in Module 1, Section 1.0.7 General Note to Reviewer. The numbered index listing should clearly highlight which components/formulations are being added to the existing components/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 as outlined in the Guidance Document Preparation of Drug Regulatory Activities in the “Non-eCTD Electronic-Only” Format.

For drug submissions and DIN applications:

Updates to MFs should be filed when the Applicant for an associated submission is required to submit a Level I - Supplement (i.e., a major Quality change) or a Level II - Notifiable Change (in the case of Biologics). At the time of filing, the update should also include any changes made in the interim period which are considered Level III - Annual Notifications in the Post-Notice of Compliance (NOC) Changes - Quality Guidance Document. This does not exempt Applicants from reporting level III changes in their annual report to Health Canada and as such, MF Holders or Authorized MF Agents should communicate these changes directly to each Applicant referencing the MF in a timely manner.

All changes to an MF should be accompanied with a side-by-side table listing the changes in comparison to the previous MF and each change should be clearly noted as being a change that falls either under Level I, II, III or IV as described by the Post-NOC Changes: Quality Guidance Document - Appendices 1-3.

All Level III changes to an MF should be filed when the next Level I or Level II changes are submitted. It is not necessary to report Level IV, however, if level IV changes are made in the documentation submitted in an MF, these should be annotated for historical purposes. Although it is not necessary to provide an update to an MF solely for Level III or Level IV changes, MF Holders or authorized MF Agents may file an update at any time. Please note, that 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)) as outlined in the Guidance Document on Post-Drug Identification Number (DIN) Changes - Appendix II: DIN Submission Types - Pharmaceuticals for Human Use and Disinfectant Drugs. MF Holders or authorized MF Agents should provide a side-by-side table listing the changes to the MF in comparison to the previous MF and each change should be clearly noted.

In addition, the MF Holder or authorized MF Agent should notify each Applicant that has been granted access to the MF in advance of implementing the change(s) so that Applicants can update their records and file the appropriate submission or PDC to Health Canada as per the conditions of the Guidance Document on Post-Drug Identification Number (DIN) Changes or Post-Notice of Compliance (NOC) Changes: Quality Document. The MF update should be filed and an MF acknowledgement letter received by the MF Holder or authorized MF Agent in

advance of Health Canada receiving the Applicant's application for the Post-DIN change or submission for the post-NOC change (e.g., Supplement, Notifiable Change).

For Clinical Trial Applications:

MF Holders or authorized MF Agents should update MFs if the previously filed information is not current. Furthermore, the MF Holder or authorized MF Agent should notify each clinical trial Applicant who has been granted access to the MF of the changes, so that sponsors can update their records and file either a CTA-A or a CTA-N to Health Canada as per the Guidance Document For Clinical Trial Sponsor: Clinical Trial Applications. The MF Update should be filed and an MF acknowledgement letter should be received by the MF Holder or authorized MF Agent in advance of Health Canada receiving the CTA-A or CTA-N by clinical trial Applicants.

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 associated with filing administrative changes to an MF.

2.4.1.1 Transfer of ownership and company name changes

MF Holders should advise Health Canada in writing if the company name or ownership of the MF has changed due to the following reasons:

- buyout
- merger
- corporate restructuring
- company name change, or
- transfer of ownership

Administrative changes should be filed to the MF Administration Unit in non-eCTD or eCTD format.

All administrative changes should be filed with a signed and dated cover letter. The cover letter should include:

- the MF Number
- the dossier ID
- the MF Type
- the reason for administrative change (i.e., transfer of ownership, company name change)
- a list of all affected MFs
- a confirmation that all LoAs remain valid
- a confirmation that all manufacturing sites and processing remain the same
- a confirmation that the previous Authorized MF Agent is still valid, if applicable

The following additional documents are also required:

- a revised MF Application Form
- an up-to-date list of all Applicants authorized to access the MF, which should be provided in Module 1, Section 1.2.6 Authorization for Sharing Information for each MF

All transfers of ownership (e.g. buyout, merger) should be filed by the new MF Holders. In addition to the requirements listed above, cover letters should include the name and address of the new MF Holder.

A transfer of ownership letter from the divesting MF Holder on company letterhead stating that it is transferring ownership of the MF to the acquiring MF Holder must be provided in Module 1, Section 1.2.9 Other Administrative Information. Transfers of ownerships should include confirmation from both the current and the new MF Holder. Any transactions for transfers of ownership received by Health Canada that are not accompanied by a transfer of ownership letter will be placed on an administrative process hold until such time as the letter has been provided.

For any administrative changes where the company name is affected, proof of the company name change (i.e. proof of incorporation or certificate of continuance) must also be provided in Module 1, Section 1.2.9 Other Administrative Information.

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, Health Canada requires 10 administrative changes to be filed (i.e., one per MF).

2.4.1.2 Change of the authorized Master File agent

If a company wishes to change the current authorized MF Agent, a letter should be provided in writing from the MF Holder to the MF Administration Unit in the proper non-eCTD or eCTD format. It is the responsibility of the MF Holder to ensure that the new appointee has all the information required (e.g., historical records). It is not the responsibility of Health Canada to provide duplicate information to a new appointee.

2.5 Withdrawal of Letters of Access

MF Holders or authorized MF Agents who wish to withdraw an authorization to reference an MF for a particular Applicant should advise the MF Administration Unit of the reasons for withdrawal of access in writing (in proper non-eCTD or eCTD format). Additionally, a list of Applicants who still have access to the MF should be provided.

The Applicant whose LoA is being withdrawn from the MF should be informed of the withdrawal of the LoA by the MF Holder or authorized MF Agent. The letter should clearly state the date after which the material will no longer be supplied to the Applicant. Substances supplied prior to the date where the LoA was withdrawn due to a supply agreement termination may still be used in authorized products according to the conditions of authorization, but the MF may no longer be referenced in subsequent applications.

Health Canada will retain the withdrawn LoA according to appropriate procedures established for record retention and disposal in accordance with the Library and Archives of Canada Act. It is understood that when an LoA is withdrawn, the previously manufactured drug substance/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 (provided in the proper non-eCTD or eCTD format) of the reason for the closure, including a statement that their obligations have been fulfilled (i.e., synthesis, manufacturing process and quality controls have been kept up-to-date and any changes that affected Applicants have been communicated to each of them and to Health Canada). On closure, MF Holders or authorized MF Agents should provide Health Canada with a list of all Applicants using the MF. It is understood that when an MF is closed, the product referred to in the MF can no longer be manufactured for use in Canadian marketed drug products. In addition, 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.

API(s) manufactured and tested in accordance with the registered procedures and manufactured and shipped to the drug product manufacturer prior to the closing of an MF can be used in Canadian marketed drug products until the stockpile is diminished or until the expiry of the API, 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 initiate post-market activities if necessary. If the reasons for closure of the MF are related to safety, the Applicant should be informed of the reasons and should contact Health Canada regarding the Health Risk Assessment and any recall actions. The MF will be retained by Health Canada according to appropriate procedures established for record retention and disposal in accordance with the Library and Archives of Canada Act. The MF may be accessed by Health Canada after closure in accordance with the law.

Health Canada will close and archive an MF that has not been assessed by Health Canada in support of a drug submission, DIN application or CTA within 5 years following the initial registration. If the MF Holder wishes to reactivate the MF with Health Canada, the MF should be filed in non-eCTD format (via CD or USB key) or in eCTD format (via the CESG). A cover letter stating the MF Holder's wish to reactivate the MF along with updates and applicable data since the date of the MF closure should be provided. The same MF number and dossier ID will be retained and fees for a New MF registration will be applied.

3. Contact information

Questions or comments related to this guidance document and to the MF process should be directed to:

Master File Administration Unit
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada
Address Locator 0201A
101 promenade Tunney's Pasture Driveway
Ottawa Ontario

K1A 0K9

Canada

Email: hc.dmf.enquiries-fmm.sc@canada.ca

Phone number: 613-941-3083

Fax number: 613-941-1668

4. References

4.1 Health Canada documents

Health Canada documents can be found on the website (<https://www.canada.ca/en/health-canada.html>).

Legislation:

- Food and Drugs Act (<http://laws-lois.justice.gc.ca/eng/acts/F-27/index.html>)
- Food and Drug Regulations (http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html)
- Medical Devices Regulations (<http://laws-lois.justice.gc.ca/eng/regulations/sor-98-282/FullText.html>)
- Access to Information Act (<http://laws-lois.justice.gc.ca/eng/acts/a-1/>)
- Library and Archives of Canada Act (<http://laws-lois.justice.gc.ca/eng/acts/L-7.7/>)

Related Guidance Documents:

- Master File Application Form (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/forms.html>)
- Guidance for Industry: Management of Drug Submissions (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry.html>)
- Guidance Document on Post-Drug Identification Number (DIN) Changes (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-drug-identification-number-changes.html>)
- Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/preparation-drug-regulatory-activities-common-technical-document-format.html>)
- Guidance Document Preparation of Drug Regulatory Activities in the “Non-eCTD Electronic-Only” Format (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html>)

- Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document Format (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/ectd/preparation-drug-submissions-electronic-common-technical-document.html>)
- Product Licence Application form (<https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/applications-submissions/product-licensing/forms-templates/product-licence-application-natural-health-products-health-canada.html>)
- Guidance for Industry Preparation of Veterinary New Drug submissions (<https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/legislation-guidelines/guidance-documents/guidance-industry-preparation-veterinary-new-drug-submissions-health-canada-2007.html>)
- Draft Guidance Document - Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/drug-products/consultation-draft-guidance-document-quality-chemistry-manufacturing-guidance-new-drug-submissions-ndss-abbreviated-new-drug-submissions.html>)
- Evidence for Quality of Finished Natural Health Products (http://publications.gc.ca/collections/collection_2007/hc-sc/H164-40-2007E.pdf)
- Post-Notice of Compliance (NOC) Changes: Quality Document (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/quality-document.html>)
- Notice: Guidance for Industry: Pharmaceutical Quality of Aqueous Solutions (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/notice-guidance-industry-pharmaceutical-quality-aqueous-solutions.html>)
- Guidance for Industry - Pharmaceutical Quality of Inhalation and Nasal Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-industry-pharmaceutical-quality-inhalation-nasal-products.html>)
- Guidance Document - Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/quality-chemistry-manufacturing-guidance-clinical-trial-applications-pharmaceuticals.html>)
- Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html>)

- Guidance for Industry: Stereochemical Issues in Chiral Drug Development (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-industry-stereochemical-issues-chiral-drug-development.html>)
- Guidance for Industry: Preparation of Quality Information for Drug Submissions in the CTD Format: Biotechnological/ Biological (Biotech) Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/guidance-industry-biotechnological-biological-biotech-products.html>)
- Preparation of the Quality Information for Drug Submissions in the CTD Format: Blood Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/guidance-industry-conventional-biotherapeutic-products.html>)
- Preparation of the Quality Information for Drug Submissions in the CTD Format: Conventional Biotherapeutic Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/guidance-industry-conventional-biotherapeutic-products.html>)
- Guidance Document Harmonized Requirements for the Licensing of Vaccines and Guidelines for the Preparation of an Application (https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demanded/guides/drugs-drogues/ctd_vaccin-eng.pdf)
- Guidance Document: Submission and Information Requirements for Extraordinary Use New Drugs (EUNDs) (https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demanded/guides/eund-dnue-eng.pdf)
- Health Canada Good Manufacturing Practices (GMP) Guidelines (<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/good-manufacturing-practices-guidelines-2009-edition-version-2-0001.html>)
- Health Canada Annex to the Good Manufacturing Practices Guidelines and Good Manufacturing Practices (GMP) for Positron Emitting Radiopharmaceuticals (PERs) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/annex-manufacturing-practices-positron-emitting-radiopharmaceuticals.html>)
- Cleaning Validation Guidances (<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/cleaning-validation-guidelines-guide-0028.html>)
- Process Validation: Aseptic Processes for Pharmaceuticals (<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/aseptic-processes-pharmaceuticals.html>)

- Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labelers, Distributors and Importers (<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/validation-documentation-requirements-responsibilities-drug-fabricators-packagers-labelers.html>)
- Validation Guidelines for Pharmaceutical Dosage Forms (<https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/validation-guidelines-pharmaceutical-dosage-forms-0029.html>)
- Guidance Document: Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans (08/15) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/guidance-document-preparation-clinical-trial-applications-use-cell-therapy-products-humans.html>)
- Guidance Document: Plant Molecular Farming (PMF) Applications: Plant -Derived Biologic Drugs for Human Use (05/14) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/plant-molecular-farming-plant-biologic-drugs.html>)
- Guidance for Industry: Stereochemical Issues in Chiral Drug Development (02/00) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-industry-stereochemical-issues-chiral-drug-development.html>)

4.2 International Council on Harmonisation guidelines

- Q1A(R2): Stability Testing of New Drug Substances and Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/stability-testing-new-drug-substances-products-topic.html>)
- Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/stability-testing-photostability-testing-new-drug-substances-products.html>)
- Q1C: Stability Testing Requirements for New Dosage Forms (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/stability-testing-requirements-new-dosage-forms.html>)
- Q1D: Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/bracketing-matrixing-designs-stability-testing-new-drug-substances-products-topic.html>)

- Q1E: Evaluation of Stability Data (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/industry-evaluation-stability-data-topic.html>)
- Q2(R1): Validation of Analytical Procedures: Text and Methodology (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/validation-analytical-procedures-text-methodology.html>)
- Q3A(R): Impurities in New Drug Substances (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/impurities-new-drug-substances-topic.html>)
- Q3B(R): Impurities in New Drug Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/industry-impurities-new-drug-products-topic.html>)
- Q3C: Impurities: Guideline for Residual Solvents (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/notice-q3cr6.html>)
- Q3D: Guideline for Elemental Impurities (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/guideline-elemental-impurities.html>)
- Q5A(R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>)
- Q5B: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/quality-biotechnological-products-analysis-expression-construct-cells-used-production-derived-protein-products-topic.html>)
- Q5C: Stability Testing of Biotechnological/ Biological Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/quality-biotechnological-products-stability-testing-biotechnological-biological-products-topic.html>)
- Q5D: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/derivation-characterisation-cell-substrates-used-production-biotechnological-biological-products-topic.html>)

- Q5E: Comparability of Biotechnological/ Biological Products Subject to Changes in their Manufacturing Process (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/comparability-biotechnological-biological-products-subject-changes-their-manufacturing-process-topic.html>)
- Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/specifications-test-procedures-acceptance-criteria-new-drug-substances-new-drug-products-chemical-substances-topic.html>)
- Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/specifications-test-procedures-acceptance-criteria-biotechnological-biological-products-topic.html>)
- Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients (<https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/compliance-enforcement/draft-guidance-good-manufacturing-practices-active-pharmaceutical-ingredients-apis-guidelines-0104.html>)
- Q7 Q&As: Questions and Answers: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/adoption-international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-guidance.html>)
- Q8(R2): Pharmaceutical Development (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/pharmaceutical-development-topic.html>)
- Q9: Quality Risk Management (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/adoption-international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use.html>)
- Q10: Pharmaceutical Quality System (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/adoption-international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-guidance-pharmaceutical-quality-system.html>)

- Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/ Biological Entities) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/development-manufacture-drug-substances-chemical-entities-biotechnological-biological-entities-topic.html>)
- Questions and Answers on Q11 (<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html#11-2>)
- M4(R3): Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (<http://www.ich.org/products/ctd.html>)
- M4Q(R1): The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality (<http://www.ich.org/products/ctd.html>)
- M8: Electronic Common Technical Document (eCTD) (<http://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html>)

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 (<http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/pharma-stability.html>)
- GL4: Stability Testing: Requirements for New Dosage Forms (<http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/pharma-stability.html>)
- GL5: Stability Testing: Photostability Testing of New Drug Substances and Products (<http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/pharma-stability.html>)
- GL8: Stability Testing for Medicated Premixes (<http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/pharma-stability.html>)
- GL10(R): Impurities in New Veterinary Drug Substances (<http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/impurities.html>)
- GL11(R): Impurities in New Veterinary Medicinal Products (<http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/impurities.html>)
- GL17: Stability Testing of New Biotechnological / Biological Veterinary Medicinal Products (<http://www.vichsec.org/guidelines/biologicals/bio-quality/stability.html>)
- GL18: Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances and Excipients (<http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/impurities.html>)
- GL39: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances (<http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/pharma-specifications.html>)

- GL40: Test Procedures and Acceptance Criteria for New Biotechnological / Biological Veterinary Medicinal Products (<http://www.vichsec.org/guidelines/biologicals/bio-quality/specifications.html>)
- GL45: Bracketing and Matrixing Designs for Stability Testing of New Veterinary Drug Substances and Medicinal Products (Step 4) (<http://www.vichsec.org/guidelines/pharmaceuticals/pharma-quality/pharma-stability.html>)

5. Appendices

Appendix 1: Relevant addresses

Appendix 2: Sample - Letter of Access

Appendix 3: Sample - Agent authorization

Appendix 4: Sample - CEP attestation letter

Appendix 1 – Relevant addresses

Pharmaceutical Drugs

Bureau of Pharmaceutical Sciences (BPS)
Therapeutic Products Directorate
Health Products and Food Branch
Health Canada
Address Locator: 0201D
Ottawa, Ontario
K1A 0K9

E-mail: hc.bps.enquiries.sc@canada.ca
Telephone: 613-941-3184
Fax: 613-941-0571

Office of Clinical Trials (OCT)

Therapeutic Products Directorate
Health Products and Food Branch
Health Canada
Address Locator: 3105A
Ottawa, Ontario
K1A 0K9

E-mail: hc.oct.enquiries-requetes.bec.sc@canada.ca
Fax: 613-946-7996

Biologic and Radiopharmaceutical Drugs

Office of Regulatory Affairs
Biologics and Genetic Therapies Directorate
Health Canada
100 Eglantine Driveway
Address Locator: 0601C
Ottawa, Ontario
K1A 0K9

E-mail: hc.bgtd.dgo.enquiries.sc@canada.ca
Fax: 613-946-9520

Appendix 2: Sample - Letter of Access

(Date)

Master File Administration Unit
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada
Finance Building, 2nd Floor
Address Locator: 0201A
101 promenade Tunney's Pasture Driveway
Ottawa, Ontario
K1A 0K9

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 Therapeutic Products Directorate or Biologics and Genetic Therapies 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 3: Sample - Agent authorization

(Date)

Master File Administration Unit
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada
Finance Building, 2nd Floor
101 promenade Tunney's Pasture Driveway
Ottawa, Ontario
K1A 0K9

Dear Sir or Madam:

Re: Master File Agent Authorization - (Master File Name) MF # (YYYY-XXX)

Please be advised that we have appointed (Company Name/Name) to be our authorized Master File Agent for the Canadian market. (Company Name/Name) will be responsible for:

- a) issuing letters of access;
- b) handling deficiencies;
- c) handling the payment of fees;
- d) handling associated correspondence; and
- e) filing updates and administrative changes.

Yours sincerely,

(Signature)

Appendix 4: Sample - CEP attestation letter

(Date)

Master File Administration Unit
Resource Management and Operations Directorate
Health Products and Food Branch
Health Canada
Finance Building, 2nd Floor
101 promenade Tunney's Pasture Driveway
Ottawa, Ontario
K1A 0K9

Dear Sir or Madam:

Re: Drug Substance - CEP # XXXXXXXXXXXXXXX

On behalf of [API Manufacturer Name/MF Holder], I attest to the following:

1. I authorise Health Canada to refer to the CEP along with Report A and the specifications authorised 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 authorised 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 and that 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.

Signed by [Authorised representative name]
[Position title]
[API Manufacturer Name]

- ¹ The terminology used in this guidance document is the same as used in the ICH guidelines. Where terminology is not defined in this section, the reader is referred to these guidelines.
- ² MFs will be placed on Process Hold until the MF is considered complete.