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GUIDANCE DOCUMENT

Master Files (MFs) - Procedures and Administrative Requirements

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Health Products and Food Branch

Canada 

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>The Health Products and Food Branch's (HPFB) mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by:</p> <ul style="list-style-type: none"> • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada's 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.

Document Change Log

Version	Guidance For Industry Master Files (MFs) - Procedures and Administrative Requirements	Replaces	Draft Guidance Document - Drug Master Files (DMFs)
Date	May 1, 2017	Date	September 5, 2008
Change			
		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.	

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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 MFs including administrative changes, updates, withdrawals and closures.

1.1 Policy Objective

To provide direction on the procedures that allow MF Holders 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 Format*, MFs are categorized as regulatory transactions (refer to Section 1.4 for definition).

They 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, 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.

The LoA is signed by the MF Holder 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; 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 (DINAs and DINBs-(B)), 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 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:

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

exception of gelatin), adjuvants (except for alum), albumin, 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.

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 - The letter accompanying the MF which explains the purpose and content of the package provided to Health Canada.

Dosage Form - A pharmaceutical product type [for example (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.

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.

Drug Substance (Active Pharmaceutical Ingredient (API)) - 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 sponsor 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 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 Pharmacopoeia (CEPs). For the purpose of this document, and in keeping with international best practices, the term MF is used.

2. GUIDANCE FOR IMPLEMENTATION

2.1 Health Canada Master Files

An MF is submitted by the MF Holder 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 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 and indicates to Health Canada that the MF Holder have 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 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).

For Type I and Type IV MFs, the MF should include the Applicant and the Restricted Parts. In addition, MFs are expected to enclose:

- A copy of a Quality Overall Summary (QOS) in Word format.
- The Certified Product Information Document (CPID) in Word format. The CPID template can be adapted to provide only the sections relevant to the manufacture and control of the drug substance and included with the Type I MF.

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. 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 MFs will be placed on Process Hold until the MF is considered complete.

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. A Type I MF may contain information on different products in accordance with Section 2.1.10 *When to File a New MF Registration*. A Type II and Type III MF may contain information on different products within a family of products (e.g., for stoppers manufactured using the same formulation). A Type IV MF 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 in the MFs 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 an MF name that distinguishes the MF from any previously registered MFs.

2.1.4 Format and Structure of the Master File

As of January 1st 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* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ctd/gd_prep_non_ectd_ld-eng.php) 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* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/annonce-annonce/notice_dmf_prep_fmm_avis_non_ectd-eng.php) for additional information on electronic filing of MFs.

MF Holders 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* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ctd/ctd_prep_nds-eng.php). Prior to filing an eCTD MF, MF Holders should contact Health Canada via email to ereview@hc-sc.gc.ca.

All documents should be provided in Portable Document Format (PDF) or in Microsoft Word. Documents may also be provided in Microsoft Excel 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 version. Any MFs that have not been converted into a non-eCTD or eCTD electronic format will be closed (no further access for assessment will be granted and no updates will be accepted). If the MF Holder wishes to reactivate the 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 closure). The same MF number will be retained and fees for a New MF registration will be applied.

MF Holders may also convert their MFs from non-eCTD to eCTD format. As a baseline requirement when converting MFs from non-eCTD format to eCTD format, the MF Holder must include the entire MF in their first eCTD transaction. It is not sufficient to convert the MF into 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 a MF has been filed in or converted into eCTD format, all subsequent transactions must also be filed in eCTD format via the CESG. Any subsequent transactions filed in 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

An MF should be filed to OSIP's MF Administration Unit:

Master File Administration Unit
Therapeutic Products Directorate
Health Products and Food Branch
Finance Building, 2nd Floor
Address Locator: 0201A
101 promenade Tunney's Pasture Driveway
Ottawa, Ontario
K1A 0K9
Email: dmf-fmm@hc-sc.gc.ca
Fax number: 613-941-0825

When preparing new MF transaction(s) in eCTD format, please submit the transaction via the CESG.

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

2.1.6.1 Shipping/Customs Information

MF Holders 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 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 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.

2.1.7.2 Filing an Letter of Access

A separate LoA is required for each Applicant who cross-references the MF in their drug submission, DIN application or CTA and each letter is subject to the applicable fees. An LoA needs to be signed by the MF Holder or Authorized MF Agent. The LoA should be sent to Health Canada and the Applicant prior to filing their drug submission, DIN application or CTA.

For Type I and IV MFs, an LoA is for an MF in its entirety and is valid for all products from the Applicant cross-referencing the MF. Therefore, only one LoA is required per applicant for an MF’s lifetime.

For Type II or III MFs, an LoA can be filed to grant access for an entire MF or specific components within an MF. Only one LoA is required per Applicant, if granting access to the entire MF or for multiple components within an MF. When granting access for an additional component, not included in the first LoA, a new LoA is required with the applicable fee.

For MFs that reference other MFs, MF Holders or Authorized MF Agents are required to file an LoA granting another MF Holder access to their MF. When an MF Holder is filing a Type IV MF that references a Type I MF, the MF Holder for the Type I MF must file an LoA granting access to the MF Holder of the Type IV MF. Separate LoAs must be filed granting the Applicant access to the Type I and to the Type IV MF as well.

As stated in Section 2.1.11, 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 company name, the MF Holder or Authorized MF Agent may submit a letter stating 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 changes where no new LoAs are issued.

Please contact OSIP's 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, a copy of the declaration of access section in a CEP or 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 of a CTA or for only specified phases. 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 OSIP's 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 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 OSIP's 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 a MF when the MF is not completely identical to the CEP dossier, but if differences between the MF and the CEP dossier exist, these differences should be clearly declared and a side-by-side comparison of the MF and CEP provided.

Stakeholders are requested to consult the Health Canada website for current information on the acceptance of CEPs.

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 on 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 a North American MF Agent be used in order to expedite communications. An Authorized MF Agent may perform all functions listed in this guidance document on behalf of the MF Holder after they have been appointed by the MF Holder.

2.1.10 When to File a New Master File Registration

The examples below indicate the criteria representing when a New Type I MF registration is required:

- 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).

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.

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 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)* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/costs-couts/crpay_rcfrais_for-eng.php).

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).

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) is sent to the designated MF contact person (MF Holder or Authorized MF Agent) as listed on the MF Application Form.

If required information, forms or fees are missing or incomplete, or provided in the incorrect format, the MF will be placed on Administrative Hold, in which case OSIP's MF Administration Unit will issue an MF transaction rejection 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.

There are two categories of Administrative Holds:

A. Process Hold

OSIP's 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 being shredded. 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, OSIP's 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 returned to the sender at their expense.

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 in the MF registration will be processed by OSIP's 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

- *Draft Guidance Document - Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)* (http://www.hc-sc.gc.ca/dhp-mps/consultation/drug-medic/consult_qual-eng.php)
- *Guidance Document - Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/qual_cta_dec-eng.php)
- *Certified Product Information Document - Chemical Entities CPID-CE* (http://hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/templates-modeles/cpidce_dcipece-eng.php)

For biologics

- *Preparation of the Quality Information for Drug Submissions in the CTD Format: Biotechnological/ Biological (Biotech) Products* (http://www.hc-sc.gc.ca/dhp-mpps/brgtherap/applic-demanded/guides/qualit/prod/tech-doc-biologic/ctd_biotech-eng.php)
- *Preparation of the Quality Information for Drug Submissions in the CTD Format: Blood Products* (http://www.hc-sc.gc.ca/dhp-mpps/brgtherap/applic-demanded/guides/qualit/prod/tech-doc-biologic/ctd_convbio-eng.php)
- *Preparation of the Quality Information for Drug Submissions in the CTD Format: Conventional Biotherapeutic Products* (http://www.hc-sc.gc.ca/dhp-mpps/brgtherap/applic-demanded/guides/qualit/prod/tech-doc-biologic/ctd_convbio-eng.php)
- *Preparation of the Quality Information for Drug Submissions in the CTD Format: Vaccines* (http://www.hc-sc.gc.ca/dhp-mpps/brgtherap/applic-demanded/guides/qualit/prod/tech-doc-biologic/ctd_vacc-eng.php)
- *Blank Certified Product Information Document (Schedule D Drugs) (CPID (Schedule D Drugs)) Template in the CTD Format* (http://www.hc-sc.gc.ca/dhp-mpps/brgtherap/applic-demanded/guides/qualit/prod/tech-doc-biologic/ctd_cpid-dcip_schd-ann-eng.php)
- *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* (http://www.hc-sc.gc.ca/dhp-mpps/brgtherap/applic-demanded/guides/radiopharm/qisr-sdqr_guide-eng.php)

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 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 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 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, and the Applicant will be notified in writing. The Applicant should ensure a timely response is sent by the MF Holder. 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* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.php).

2.3.3 Responses to Clarification requests

The responses to clarification requests and Letters of Deficiencies in non-eCTD format must be sent to OSIP's MF Administration Unit as per the *Guidance Document Preparation of Drug Regulatory Activities in the "Non-eCTD Electronic-Only" Format*³. For eCTD MFs, responses must be submitted as a new sequence through the CESG, in addition to providing the official copy.

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.

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: OPPRS_enquiries@hc-sc.gc.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 OSIP's 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, Post-Notice of Compliance (NOC) Changes - Quality Guidance Document* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/postnoc_change_apresac/noc_pn_quality_ac_sa_qualite-eng.php) or *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 and appropriate fees.

A single electronic copy of the update should be filed with a signed 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:

- 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.

When filing an update to an MF (Type II and Type III MF) 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 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.

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 may file an update at anytime. 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 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 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 Post-DIN Guidance Document or Post-NOC Changes Quality Guidance 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 should update MFs if the previously filed information is not current. Furthermore, the MF Holder 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

For a transfer of ownership and a company name change of an MF, the original MF Holder should advise Health Canada in writing if ownership or the name of the MF has changed due to the following reasons:

- Buyout;
- Merger;
- Corporate restructuring;
- Company name change; or
- Any other reason for a transfer of ownership.

The following documentation should be provided electronically:

- A cover letter from current MF Holder (or Authorized MF Agent, if applicable) with name and address of the new MF Holder;
- The new MF Holder should concurrently provide a letter accepting transfer of ownership (not applicable for a company name change);
- Proof of the company name change (i.e., proof of incorporation or certificate of continuance);
- A list of all affected MFs;
- A confirmation that all LoAs remain valid;
- An up-to-date list of all Applicants authorized to access the MF;
- A confirmation that all manufacturing sites and processing remain the same;
- A confirmation that the previous Authorized MF Agent is still valid, if applicable;
- A revised MF Application Form.

All transfers of ownerships should include confirmation from both the current MF Holder and the new MF Holder. It is not acceptable for Health Canada to receive notice of the transaction from only the new MF Holder.

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 OSIP's 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 who wish to withdraw an LoA for a particular Applicant to reference an MF should advise OSIP's MF Administration Unit in writing (in proper non-eCTD or eCTD format) of the reasons for withdrawal of access and provide a list of Applicants who still have access to their MF.

The Applicant whose LoA is being withdrawn from the MF should be informed of the withdrawal of the LoA by the MF Holder. 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 OSIP's 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 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 (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 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:

Health Canada
Health Products and Food Branch
Therapeutic Products Directorate
Master File Administration Unit
Address Locator 0201A
101 promenade Tunney's Pasture Driveway
Ottawa Ontario
K1A 0K9
Canada

Email: dmf-fmm@hc-sc.gc.ca
Fax number: 613-941-0825

4. REFERENCES

4.1 Health Canada Documents

Health Canada documents can be found on the website (<http://www.hc-sc.gc.ca>).

Legislation:

- Food and Drugs Act (<http://laws-lois.justice.gc.ca/eng/acts/f-27/>)
- 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 (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/index-eng.php>)

- Guidance for Industry: Management of Drug Submissions (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/mgmt-gest/mands_gespd-eng.php)
- Guidance Document on Post-Drug Identification Number (DIN) Changes (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/change_din-eng.php)
- Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ctd/ctd_prep_nds-eng.php)
- Guidance Document Preparation of Drug Regulatory Activities in the “Non-eCTD Electronic-Only” Format (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/annonce-annonce/notice_avis_app_din_non_ectd-eng.php)
- Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document Format (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ectd/prep_ectd_format-eng.php)
- Product Licence Application form (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/form/form_pl-dlmm-eng.php)
- Guidance for Industry Preparation of Veterinary New Drug submissions (http://www.hc-sc.gc.ca/dhp-mps/vet/legislation/guide-ld/vdd_nds_guide-eng.php)
- Draft Guidance Document - Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (<http://www.hc-sc.gc.ca/dhp-mps/consultation/drug-medic/qual-ndsands-draft-ebauche-pdnpadn-eng.php>)
- 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 (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/postnoc_change_apresac/noc_pn_quality_ac_sa_qualite-eng.php)
- Notice: Guidance for Industry: Pharmaceutical Quality of Aqueous Solutions (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/chem/aqueous_aqueuses-eng.php)
- Guidance for Industry - Pharmaceutical Quality of Inhalation and Nasal Products (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/chem/inhalationnas-eng.php>)
- Guidance Document - Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/clini/qual_cta_dec-eng.php)
- Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/clini/ctdcta_ctddec-eng.php)

- Guidance for Industry: Stereochemical Issues in Chiral Drug Development (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/stereo-eng.php>)
- Guidance for Industry: Preparation of Quality Information for Drug Submissions in the CTD Format: Biotechnological/ Biological (Biotech) Products (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd_biotech-eng.php)
- Guidance Document: Submission and Information Requirements for Extraordinary Use New Drugs (EUNDS) (<http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/eund-dnue-eng.php>)
- Health Canada Good Manufacturing Practices (GMP) Guidelines (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>)
- Health Canada Annex to the Good Manufacturing Practices Guidelines and Good Manufacturing Practices (GMP) for Positron Emitting Radiopharmaceuticals (PERs) (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui_0071_tc-tm-eng.php)
- Cleaning Validation Guidances (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui_0028_tc-tm-eng.php)
- Process Validation: Aseptic Processes for Pharmaceuticals (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/app-papp-eng.php>)
- Guidance for Industry: Product- Specific Facility Information (<http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/info/index-eng.php>)
- Site Reference File Guideline
- Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/ Labellers, Distributors and Importers (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/req_resp-exig_resp_tc-tm-eng.php)
- Validation Guidelines for Pharmaceutical Dosage Forms (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui_29-eng.php)
- Guidance - Regulatory Requirements to Minimize the Risk of Transmission of Transmissible
- Guidance Document: Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans (08/15) (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cell-therapy-therapie-cellulaire-eng.php>)
- Guidance Document: Plant Molecular Farming (PMF) Applications: Plant -Derived Biologic Drugs for Human Use (05/14) (<http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/pmf-mcv-eng.php>)
- Guidance for Industry: Stereochemical Issues in Chiral Drug Development (02/00) (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/stereo-eng.php>)

4.2 International Council on Harmonisation Guidelines

- Q1A(R2): Stability Testing of New Drug Substances and Products ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1a\(r2\)-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1a(r2)-eng.php))
- Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1b-eng.php>)
- Q1C: Stability Testing Requirements for New Dosage Forms (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1c-eng.php>)
- Q1D: Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1d-eng.php>)
- Q1E: Evaluation of Stability Data (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q1e-eng.php>)
- Q2(R1): Validation of Analytical Procedures: Text and Methodology (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q2r1-eng.php>)
- Q3A(R): Impurities in New Drug Substances ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q3a\(r\)-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q3a(r)-eng.php))
- Q3B(R): Impurities in New Drug Products ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q3b\(r\)-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q3b(r)-eng.php))
- Q3C: Impurities: Guideline for Residual Solvents (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q3c-eng.php>)
- Q3D: Guideline for Elemental Impurities (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q3d-step4etape-eng.php>)
- Q5A(R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (<http://www.ich.org/>)
- Q5B: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q5b-eng.php>)
- Q5C: Stability Testing of Biotechnological/ Biological Products (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q5c-eng.php>)
- Q5D: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q5d-eng.php>)
- Q5E: Comparability of Biotechnological/ Biological Products Subject to Changes in their Manufacturing Process (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q5e_step4_etape4-eng.php)
- Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/ich/qual/q6a-step4etape-eng.php>)

- Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q6b-eng.php>)
- Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients (<http://www.hc-sc.gc.ca/dhp-mps/consultation/compli-conform/2012-gui-0104-eng.php>)
- Q7 Q&As: Questions and Answers: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (<http://www.ich.org/>)
- Q8(R2): Pharmaceutical Development (<http://www.ich.org/>)
- Q9: Quality Risk Management (<http://www.ich.org/>)
- Q10: Pharmaceutical Quality System (<http://www.ich.org/>)
- Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/ Biological Entities) (<http://www.ich.org/>)
- Questions and Answers on Q11 [to be added when posted]
- M4(R3): Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (<http://www.ich.org/>)
- M4Q(R1): The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality
- M8: Electronic Common Technical Document (eCTD)

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
Address Locator: 0201D
Health Canada
Ottawa, Ontario
K1A 0K9

E-mail: bps_enquiries_enquetes_bsp@hc-sc.gc.ca
Telephone: 613-941-3184
Fax: 613-941-0571

Office of Clinical Trials (OCT)
Therapeutic Products Directorate
Health Products and Food Branch
Address Locator: 3105A
Health Canada
Ottawa, Ontario
K1A 0K9

E-mail: OCT_BEC_Enquiries_Enquetes@hc-sc.gc.ca
Fax: 613-946-7996

Biologic and Radiopharmaceutical Drugs

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

E-mail: BGTD_ORA@hc-sc.gc.ca
Fax: 613-946-9520

APPENDIX 2: SAMPLE - LETTER OF ACCESS

(Date)

Master File Administration Unit
Therapeutic Products Directorate
Health Products and Food Branch
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)

APPENDIX 3: SAMPLE - AGENT AUTHORIZATION

(Date)

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

Dear Sir or Madam:

RE: *Drug Substance* - CEP # XXXXXXXXXXXXXXXX

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]