Health Canada Santé Canada

February 15, 2016

Notice

Our file number: 16-101401-306

Draft Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements

Health Canada is pleased to announce the release of the revised *Draft Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements* for external consultation only.

The 2008 *Draft Guidance Document - Drug Master Files (DMFs)* is outdated and not in line with international efforts to standardize MF terminology and MF procedures. The revised draft 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. It also introduces process changes that are less cumbersome on industry and Health Canada.

Changes to the revised draft include:

- Revised terminology such as the use of master file, applicant's part and restricted part, incorporating IGDRP criteria for the issuance of new master files and adopting International Council for Harmonisation (ICH) definitions.
- Adding clinical trial specific processes.
- Clarifying the requirements for Letters of Access that are now specific for the MF or MF component (rather than for a product line).
- Clarifying timelines for responding to requests for additional information.
- Requesting that MFs are filed no more than one year but no less than 2 months prior to filing of a drug submission or clinical trial application (CTA) making reference to those MFs.
- Encouraging filing of Certificates of Suitability (CEP)s.
- Clarification of the timelines and procedures surrounding changes to the MF. All quality changes to MFs are now called updates and these are only required when a Supplement to an Abbreviated New Drug Submission [(A)NDS], Notifiable Change (for biologics), CTA-Amendment or CTA-Notification need to be filed with Health Canada.
- Adding timelines for closure and disposal of an MFs if it is not assessed after 5 years.

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- Clarifying the procedures surrounding closure of an MF and indicating that Health Canada can close an MF due to lack of reference.
- Renaming the Fee Form to "MF Fee Form".

As a consequence of some of these changes, fees charged for the provision of non-regulatory MF services and the corresponding service standards are being reassessed. Any proposed changes to the fees or service standards will be communicated to industry stakeholders.

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

Health Canada
Health Products and Food Branch, Therapeutic Products Directorate
Bureau of Policy, Science and International Programs
Address Locator 3102C3
Holland Cross, Tower B
1600 Scott St.
Ottawa, Ontario
K1A 0K9

Telephone: 613-948-4623
Email: policy_bureau_enquiries@hc-sc.gc.ca

Health Canada Santé Canada

DRAFT GUIDANCE DOCUMENT

Master Files (MFs) – Procedures and Administrative Requirements

This guidance document is being distributed for comment purposes only.

Published by authority of the
Minister of Health

Draft Date	2016/02/10

Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's (HPFB) mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by: • 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. *Health Products and Food Branch*

Également disponible en français sous le titre : Ébauche de la ligne directrice : Fiches maîtresses (FM) - Procédures et exigences administratives

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	Draft Guidance For Industry Master Files (MFs) – Procedures and Administrative Requirements	**Replaces**	Draft Guidance Document - Drug Master Files (DMFs)
Date	February 5, 2016	**Date**	September 5, 2008
Change		February 10, 2016 Some revisions throughout the document	
Nature of and/or Reason for Change		The revised draft 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 of a proprietary nature [that is (i.e.), confidential business information] and is not available to the manufacturer of the dosage form or to the sponsors of a drug submission or clinical trial application (hereafter referred to as the applicants).

The federal government is required by law to assure that confidential business information (CBI) is not given to unauthorized recipients. As a result, Health Canada's policy, outside the Access to Information Act, prevents it from providing CBI contained in an MF to anyone other than the MF Holder or Authorized MF Agent. Information in the Applicant's part of an MF (formerly the Open Part) can only be discussed with applicants to whom access has been provided in writing.

This guidance provides MF related-definitions, information on filing requirements, processing and assessment procedures related to Type I to IV MFs and outlines the registration requirements for MF applications including closures, withdrawals, updates, and administrative changes.

1.1 Policy Objective

To provide guidance and direction on the procedures that allows MF Holders to file CBI directly with Health Canada that may be referenced to support an applicant's drug submission or clinical trial application (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 the relevant non-proprietary information provided by the MF Holder, obtained in the public domain, and/or developed by the applicant in the drug submission or clinical trial application (CTA).

The applicants should ensure that the information included in the MF is up to date and that the MF has been received by Health Canada.

The 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 from the MF Holder.

1.3 Scope and Application

This guidance document applies to all MF Holders, applicants using an MF to support drug submissions for human use or CTAs and Health Canada employees involved in MF processes. Submissions and applications include New Drug Submissions (NDSs), Abbreviated New Drug Submissions (ANDSs), Supplements to New Drug Submissions (SNDS) or Supplemental Abbreviated New Drug Submissions (SANDS), Applications for Drug Identification Numbers (DINAs and DINBs-(B)), Notifiable Changes (NC) (in the case of biologics), Post-Authorization Division 1 Changes for biologics (PDC-B), Post-DIN Changes for pharmaceuticals, early Biologic Product Reports (YBPR), CTAs and CTA-Amendments (CTA-A). MFs may be referenced by more than one applicant.

The guidance also applies to MF Holders intending to file MFs that are cross-referenced in drug submissions 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 does not apply to MFs used in support of natural health products (NHPs) subject to the *Natural Health Products Regulations.* For NHP Master Files, 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 *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*
For pharmaceuticals Drug substance or intermediate in the manufacture of a drug substance. This can include Active Pharmaceutical Ingredients (API). *For biologics* Drug substance can include bulk process intermediates, vaccine antigens, excipients of biological origin (with the exception of gelatin),	Container closure systems (CCS) or CCS components.	Excipients, capsule shells, coating ingredients, colourants, flavours, and other additives, including alum and growth media.	Dosage forms and drug product intermediates.

adjuvants (except for alum), albumin, critical raw materials for radiopharmaceuticals or vectors for gene therapy.			

1.4 Definitions[1]

Applicant - The company submitting an NDS, ANDS, SNDS, SANDS, DINA or DINB, NC, PDC-B, YBPR, CTA or CTA-A. 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 a 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 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 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 - 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 permitting Health Canada to access the information contained in the MF on behalf of the applicant.

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 owns the MF. This may be the manufacturer of the product described in the MF and/or the owner of the confidential business information.

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

Person(s) - Individuals, partnerships, corporations or associations.

Regulatory Activity - a collection of all regulatory transactions throughout the process of a specific activity which includes, but is not limited to, NDS, ANDS, DIN Application, CTAs, 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 confidential business information contained in a 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

Health Canada is the Federal department responsible for helping Canadians maintain and improve their health. Health Canada plays an active role in ensuring the access to safe, effective, and high quality drugs and health products.

The principles outlined in this guidance document are intended to create greater alignment with the procedures used internationally for the management of Master Files (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. The 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 Files is used.

2. GUIDANCE FOR IMPLEMENTATION

2.1 Health Canada Master Files (MFs)

Type I ASMFs and Type IV Dosage Form Master Files are divided in two parts: the "Restricted Part" and the "Applicant's Part" which is provided to the Applicant and is usually included as part of the applicants drug submission or clinical trial application (CTA), with the accompanying Letter of Access (LoA).

For Type I ASMFs, the Applicant's Part contains the information that the ASMF Holder regards as non-confidential to the applicant, whereas the Restricted Part contains the information that the ASMF Holder regards as confidential. An MF will not be considered complete if both parts have not been provided to Health Canada.

The LoA is signed by the MF Holder and grants Health Canada permission to assess the information provided in the MF during the assessment of the applicant's drug submission or CTA. The Restricted Parts are filed by the MF Holder to Health Canada directly. An MF is submitted by the MF Holder only in cases where the company does not wish to disclose confidential business information (CBI) to the applicant of the drug submission or CTA.

2.1.1 Confidentiality

Within Health Canada, MFs are kept confidential and only officials of Health Canada have permission to access these records. Therefore, data and other scientific or technical information are assessed and filed in strict confidence. In legal terms, this CBI belongs to the suppliers that generate it and has traditionally been protected by intellectual property law. In Canada, intellectual property includes, in part, patents, trademarks, copyright and trade secrets.

However, submitted information which objectively qualifies as CBI is subject to the federal *Access to Information Act* [http://laws-lois.justice.gc.ca/eng/acts/a-1/] when there is a formal request made under that Act. Section 20 of the Act protects information that qualifies as third party commercial, scientific or technical information and is a mandatory exemption, which means that government institutions must not disclose certain third party information. This is true whether the circumstance is the provision of information

for the public, such as adverse drug reaction or for a regulatory decision document, or when the drug product information is subject to an access to information request.

Section 20 of the *Access to Information Act* gives the government the authority to refuse to disclose information that meets the requirements in this section as is often the case for applicants and/or MF Holders information. It effectively defines the scope of "third party confidential information" that accords persons certain rights and protections with respect to information under the control of a government institution.

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 or clinical trial application making reference to those MFs. All MFs are expected to include at least one letter of access when filed.

For New MF Registrations the following electronic documents are required:

- One signed cover letter, including the MF name
- MF Agent Authorization Letter from MF Holder, if applicable
- MF Application Form
- Master File Fee Form and appropriate fees
- Certificate of Suitability (CEP) and Attestations (for Type I MFs only), if applicable
- Letter(s) of Access (see section 2.3.2)

For Type I ASMFs and Type IV Dosage Form Master Files, the following additional electronic documents are required:

- The MF must include the Applicant and the Restricted Parts
- A Copy of Quality Overall Summary (QOS) in Word format
- The Certified Product Information Document (CPID) in Word format, if applicable.

For Type II CCS MFs and Type III Excipient 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. 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 and the Restricted Parts.

Of note, Health Canada does not approve MF registrations. 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 an MF

For Type I ASMFs, the preferred name of the MF should be the generic name (e.g., the International Nonproprietary Name (INN) for an active pharmaceutical ingredient) followed by any manufacturer's internal API brand names or codes to identify a particular product. If applicable, any counter ions, solvated states of the API should be clearly identified.

A single MF may contain information on different products in accordance with section 2.1.10 for Type I MF or within a product family (e.g., for stoppers of the same formulation). A Type IV Dosage Form Master File 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 Dosage Form Master Files.

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. 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 MF

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* which includes guidance on MF structure and content as well as the breakdown of the Applicant and the Restricted Parts. Also refer to the 2015 *Notice - Re: Preparation of Drug Master File (DMF) in "Non-eCTD Electronic-Only" Format*.

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*. Prior to filing an eCTD MF, MF Holders should contact Health Canada via email to ereview@hc-sc.g.ca.

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

By March 2016, all MFs previously registered with Health Canada must have filed a complete conversion to replace their paper MF with a non-eCTD or eCTD electronic version. Failure to comply and provide the electronic copy to Office of Submissions and Intellectual Property (OSIP) will result in the MF being suspended (no further access for assessment will be granted and no updates will be accepted). Once a MF is suspended

and if the MF Holder wishes to reactivate the MF, a letter should be sent to Health Canada with the converted MF in electronic format as above. Applicable fees for updating will be applied.

2.1.5 Official Language of Correspondence

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

2.1.6 Where to Send MF Registrations

An MF should be filed to the MF Administration Unit's forwarding address:
Health Canada
Health Products and Food Branch
Therapeutic Products Directorate
Master File Administration Unit
Address Locator 0201D
101 promenade Tunney's Pasture Driveway
Ottawa Ontario
K1A 0K9
Canada

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

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 confidential business information (CBI) directly with Health Canada that may be referenced to support an applicant's drug submission or CTA with respect to Quality information. The information in the MF will only be used if the MF Holder provides Health Canada with a signed original LoA to the MF Applicant. The LoA grants Health Canada permission to access the information contained in the MF.

2.1.7.1 Information to include in the LoA

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 MF
- Manufacturer's Internal Code, if applicable
- Applicant's Name being granted access to the MF
- The appropriate Master File Fee Form and Fees

2.1.7.2 LoA Filing

A separate LoA is required for each applicant who cross-references the MF in their drug submission or CTA and each letter is subject to the applicable fees. A LoA needs to be signed by the MF Holder. A copy of the LoA should be sent to the applicant prior to filing their drug submission or CTA.

For Type I and IV, a LoA is for an MF in its entirety and is valid for all products from the applicant cross-referencing the MF.

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

When a MF Holder is filing a Type IV Dosage Form Master File that references a Type I ASMF, the MF Holder for the Type I ASMF must file a LoA granting access to the MF Holder of the Type IV Dosage Form Master File. Separate LoAs must be filed granting the applicant access to the Type I ASMF and to the Type IV Dosage Form Master File as well.

As stated under section 2.1.11, the fee for the registration for a LoA is applicable to each time a LoA is filed, including when a LoA is refiled (e.g., LoAs should be refiled if the applicant's name is changed). LoAs should not be refiled if they are already on file. In these cases, MF Holders will be charged the applicable LoA fee.

Please contact OSIP prior to refiling a LoA to confirm requirements.

Note: The declaration of access section in a CEP is not equivalent to a LoA. Furthermore, a copy or the CEP should not be submitted with each LoA. See section 2.1.8 for information on submitting CEPs.

2.1.7.3 LoAs for Clinical Trials (Pharmaceutical and Biologic)

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 the MF Administration Unit with accompanying Master File Fee Form and fee. A copy should be included in the CTA or CTA-Amendment. No additional copy should be provided outside of the Applications.

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

MF Holders are encouraged to include the CEP when filing their MF with Health Canada as applicable. MF Holders are requested to confirm at the time of filing if no CEP is available.

If one is not available at the time of filing it should be provided as the CEP becomes available. Furthermore, when an updated CEP is issued it should be sent to the MF Administration Unit. All CEPs should be accompanied with the relevant attestations outlined in the notice posted on the Health Canada website (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/int/edqm_2007-eng.php). When providing an updated CEP, new attestations should be provided.

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

2.1.9 Appointment of the Authorized MF Agent

When an Agent is appointed they are responsible for all correspondence on the MF, including but not limited to the following:

- issuing Letters of Access
- 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 MF Registration

The examples below indicate the criteria representing when a New Type I (ASMF) 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.

The following examples will not necessarily be considered to represent a new ASMF and in most cases could be incorporated in a single ASMF 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 master MF should be submitted.

2.1.11 MF Fees

The administration of MFs is a non-regulatory voluntary service provided to the fee payers. Fees are collected for the registration and processing of each New MF, Letter of Access (LoA) and Update. If a LoA is refiled then the fee is applicable each time it is refiled.

Refer to the Master File Fee Form regarding fees for the processing of a New MF, LoA and Update.

Fees are increased annually by 2% on the first of April.

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 MFs

MFs are processed in sequence according to the date of receipt. When a 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 registration submissions)
- Verifying that the correct information, documents and forms have been filed 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 is sent to the designated MF contact as listed on the MF Application Form

If required information, forms or fees are missing or incomplete, the MF will be placed on Administrative Hold, in which case the Office of Submissions and Intellectual Property (OSIP) will issue an MF transaction rejection letter to the MF contact requesting the missing information.

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 and material). This hold will remain in place until the required information is submitted.

There are two categories of administrative holds:

A. Process Hold
OSIP will place the MF on Process Hold when the MF is considered incomplete, or when the information is filed as the wrong transaction type (i.e., New MF should have been filed as an Update). When the reason for the Process Hold is addressed, the MF transaction is considered administratively complete and a filing date will be applied.

B. Cost Recovery Hold
In the event that the Master File Fee Form or applicable fee is not provided or the applicable fee is insufficient, OSIP will request the fee form and payment from the MF contact. 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 issued by cost recovery, the transaction will not be accepted. When the reason for the Cost Recovery Hold is addressed, the submission is considered administratively complete and a filing date will be applied.

Failure to respond to a request for additional or corrected information in the prescribed time will result in the MF being shredded and/or closed.

2.2.2 Application and File Maintenance Requirements

All correspondence (e.g., cover letters or letters of access to an MF) should come from the MF Holder, where applicable. Any information filed by a third party will be 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 or clinical trial application referencing the MF, and is to be included in their submission/application to Health Canada.

2.2.3 MF Performance Standards

All information and material filed in the MF registration will be processed by the MF Administration Unit within 30 calendar days of receiving a complete package.

2.3 Assessment of MFs

MFs are always assessed in the context of a drug submission or clinical trial application and therefore, decisions rendered on the Quality-related data in a MF pertain to the drug seeking market authorization or clinical trial authorization.

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_dcipec-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-mps/brgtherap/applic-demande/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-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd_blood-sang_prods-eng.php)

- *Preparation of the Quality Information for Drug Submissions in the CTD Format: Conventional Biotherapeutic Products* (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/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-mps/brgtherap/applic-demande/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-mps/brgtherap/applic-demande/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-Radiopharmceuticals (CPID-R) Templates* (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/radiopharm/qisr-sdqr_guide-eng.php)

For specific information on the content of Type II CCS MFs and Type III Excipient MFs not covered in the above guidance documents, the relevant Assessment Bureau should be contacted.

2.3.1 Solicited Information

For Type I ASMFs, all non-confidential business information on the drug substance should be included in the drug submission/application. The Applicant's Part of the MF may, therefore, be subject to discussions between Health Canada and the applicant that has been granted access to reference the MF.

Outside of the Access to Information (ATI) regime, all communications with respect to the Restricted Part of the MF 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 submission/application. 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 Types I, II, III MFs, if further clarification of information is required, a 5 day clarification request will be issued to the MF Holder. 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 have 45 calendar days to respond to the Letter of Deficiency. If additional time is required, the MF Holder should contact the relevant Assessment Bureau Director to request an extension.

For Type IV Dosage Form Master Files, communications with the MF Holder will be in accordance with the *Guidance for Industry: Management of Drug Submissions*.

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 in the timeframe given to the applicant to respond to the NON.

If at the time a decision is being rendered on the applicant's submission the MF is found to be deficient, then an NON will be sent to the applicant and a Letter of Deficiency will be issued to the MF Holder (unless a letter was previously issued as outlined above).

2.3.2.1 Clarifications Requests during MF Assessment in Support of a CTA

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 sponsor will be notified in writing. The sponsor 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 Not Satisfactory Notice as per the *Guidance Document: For Clinical Trial Sponsor: Clinical Trial Applications*.

2.3.3 MF Assessment Reports

Upon completion of the MF assessment, reports may be sent to MF Holders as per Health Canada's *Guidance for Industry: Management of Drug Submissions* (refer to section 6.1 Reviewer Reports).

2.4 Updates to a Registered MF

Updates are to be filed by the MF Holder 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 Post-Notice of Compliance (NOC) Changes - Quality Guidance Document or Guidance Document: For Clinical Trial Sponsor: Clinical Trial Applications* .

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 side by side comparison of the affected sections of the MF listing the level of the change and the impact of that change
- An up-to-date list of all applicants authorized to access the MF
- A revised MF Application Form
- Master File Fee Form and fees

When filing an Update to a 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 file a current index listing all components/formulations when filing the update for the MF.

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:

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, these

changes should be communicated 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*.

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 to Health Canada as per the conditions of the *Post-NOC Changes Quality Guidance Document*. The MF Update should be filed and an acknowledgement letter received in advance of Health Canada receiving the applicant's 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 sponsor that has been granted access to the MF, of the changes so that sponsors can update their records and file either a CTA-Amendment (CTA-A) or a CTA-Notification (CTA-N)to Health Canada as per the *Guidance Document: For Clinical Trial Sponsor: Clinical Trial Applications*. The Acknowledgement Letter for the update of the MF should be received in advance of filing the CTA-A or CTA-N by clinical trial sponsors.

2.4.2 Administrative Changes

2.4.2.1 Transfer of Ownership and Company Name Changes

For a Transfer in 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:

- Buy-Out
- Merger
- Corporate restructuring
- Company Name Change
- Any other reason for a Transfer of Ownership

The following documentation should be provided electronically:

- Cover letter from current MF Holder (or Authorized MF Agent, if applicable) with name and address of the new MF Holder
- New MF Holder should concurrently provide a letter accepting transfer of ownership (not applicable for a company name change)
- Proof of company name change (i.e., proof of incorporation or certificate of continuance)
- Confirmation that all Letters of Access remain valid
- An up-to-date list of all applicants authorized to access the MF
- Confirmation that all manufacturing sites and processing remain the same
- Confirmation that the previous Authorized MF Agent is still valid, if applicable
- 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.

2.4.2.2 Change of the Authorized MF Agent

If a company wishes to change the currently Authorized MF Agent, a notification must be provided in writing from the MF Holder to Health Canada's Administration Unit. 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 a Letter of Access (LoA) for a particular applicant to reference a MF should advise Health Canada in writing of the reasons for withdrawal of access and provide a list of applicants who still have access to their MF.

The applicant whose LoA to the MF is being withdrawn 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 or will dispose of it 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 a LoA is withdrawn, the previously manufactured drug substance/material will no longer be supplied to the applicant.

2.6 MF Closures

MF Holders who wish to close a MF should notify Health Canada in writing 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 drug substance can no longer be manufactured at that site. 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 dispose of a MF that has not been assessed within 5 years of registration. If the MF Holder wishes to register the MF again with Health Canada, a new MF should be filed, with all applicable data, and a new MF number will be assigned. Applicable fees 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 0201D
101 promenade Tunney's Pasture Driveway
Ottawa Ontario
K1A 0K9
Canada

Email: HC.DMF-FMM.SC@canada.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 Guidances:

- Master File Application Form (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/dmfapp_fmmdem_2012-eng.php)
- *Guidance for Industry: Management of Drug Submissions* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-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-demande/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/applic-demande/guide-ld/ctd/gd_prep_non_ectd_ld-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-demande/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_pdnpadn_ebauche-eng.php)
- *Evidence for Quality of Finished Natural Health Products* (http://publications.gc.ca/collections/collection_2007/hc-sc/H164-40-2007E.pdf)
- *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)

- *Post-Notice of Compliance (NOC) Changes: Quality 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)
- Notice: Guidance for Industry: Pharmaceutical Quality of Aqueous Solutions (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/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-demande/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-demande/guide-ld/clini/qual_cta_dec-eng.php)
- *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)
- *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)
- PIC/S Annex 1: Explanatory Notes for Industry on the Preparation of a Site Master File (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/licences/directives/gui_0005_tc-tm-eng.php)
- 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 Spongiform Encephalopathies (TSEs) via Animal-Sourced Materials used in the Manufacture of Schedule D (Biologic) Drugs*
- *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 ICH Guidelines

- *Q1A(R2): Stability Testing of New Drug Substances and Products* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/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-demande/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-demande/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-demande/guide-ld/ich/qual/q1d-eng.php)
- *Q1E: Evaluation of Stability Data* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/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-demande/guide-ld/ich/qual/q2r1-eng.php)
- *Q3A(R): Impurities in New Drug Substances* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/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-demande/guide-ld/ich/qual/q3b(r)-eng.php)
- *Q3C: Impurities: Guideline for Residual Solvents* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/qual/q3cr5-step4etape-eng.php)
- *Q3D: Guideline for Elemental Impurities* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/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-demande/guide-ld/ich/qual/q5b-eng.php)
- *Q5C: Stability Testing of Biotechnological/ Biological Products* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/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-demande/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-demande/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-demande/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 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)