Health Canada Santé Canada

Guidance Document

Master Files for Veterinary Products: Procedures and Administrative Requirements

July 23, 2020

Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

Également disponible en français sous le titre :
Ligne directrice : Fiches maîtresses pour les produits vétérinaires : Procédures et exigences administratives

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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 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 program 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 relevant sections of other applicable Guidance documents.

Table of Contents

1. Introduction

1.1 Purpose

The objective of this guidance document is to outline the procedures that veterinary Master File (MF) holders must follow to file confidential business information[1] (CBI) directly with Health Canada's Veterinary Drugs Directorate (VDD) that is cross-referenced in support of an Applicant's veterinary drug submission (including DIN (Drug Identification Number) applications).

A MF is a reference document that provides information about specific equipment, processes or components used in the manufacturing, processing, or packaging of a drug. The MF is a useful document for providing CBI to Health Canada that is not available to the manufacturer of the dosage form or to the Applicant of a drug submission.

This guidance document provides information on filing requirements, processing and assessment procedures for veterinary MFs, and outlines the registration requirements for administrative changes, updates, withdrawals and closures. It is intended to create greater alignment with the procedures used internationally for the management of MFs.

1.2 Scope and Application

This guidance document applies to:

- Active pharmaceutical ingredient (API) manufacturers
- MF Holders intending to file MFs for veterinary products only
- Applicants using a MF to support drug submissions for veterinary use

2. About Veterinary Master Files

2.1 Purpose of a Master File

A veterinary MF is submitted by the MF Holder to Health Canada when the company does not wish to disclose CBI to the Applicant of the veterinary drug submission.

[1] "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]

MFs are always accessed and assessed in conjunction with a veterinary drug submission and, therefore, decisions on the quality-related data in a MF pertain to the drug for which market authorization is being sought.

MFs may be cross-referenced by more than one Applicant.

MF Holders who intend to file MFs that are cross-referenced in drug submissions for **both** human and veterinary use or clinical trial applications (CTA) should refer to the Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements.

2.2 Types of Master Files

MFs are classified according to the following types:

Table 1. Types of Master Files

Type I **Active Substance Master Files**	**Type II** **Container Closure System Master Files**	**Type III** **Excipient Master Files**	**Type IV** **Dosage Form Master Files**
For pharmaceuticals: Active Pharmaceutical Ingredients (API) (drug substances), starting materials or intermediates used in the manufacture of a drug substance.	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.

- Type I and Type IV MFs are divided in two parts:
    - Restricted Part (previously referred to as “closed” part): contains the information that the MF Holder regards as CBI and is filed by the MF Holder, along with the Applicant Part, to the VDD directly
    - Applicant Part (previously referred to as “open” part): contains the information that the MF Holder regards as non-confidential. It is provided to the Applicant and is included as part of the Applicant’s veterinary drug submission with the accompanying Letter of Access (LoA)
- Appendices A and B of this document outline the Restricted and Applicant Parts for Type I and Type IV MFs.
- 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 numbered index listing all the components should be included with the MF.

There is no public listing of veterinary MFs registered in Canada.

2.3 Protection and Disclosure of Master File Information

Health Canada ensures that the Restricted Part of the MF is kept confidential 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 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.

CBI contained in a MF could also be subject to the disclosure authorities in the *Food and Drugs Act*. Section 21.1(2) authorizes the disclosure of CBI about a therapeutic product where the Minister believes that the product may present a serious risk of injury to human health. Section 21.1(3) of the *Food and Drugs Act* authorizes the disclosure of CBI about a therapeutic product to a government, a person from whom the Minister seeks advice or eligible persons for the purpose of protection or promotion of human health or the safety of the public. Refer to Health Canada's Guidance Document – Disclosure of Confidential Business Information under Paragraph 21.1(3)(c) of the *Food and Drugs Act*.

2.4 Technical Requirements

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

- Guidance for Industry – Preparation of Veterinary New Drug Submissions
- Guidance Document – Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format
- Quality Overall Summary – New Drug Submissions/Abbreviated New Drug Submissions (VDD QOS (NDS/ANDS))
- Guidance for Industry – Preparation of Veterinary Abbreviated New Drug Submission – Generic Drugs
- Post-Notice of Compliance (NOC) Changes – Quality Guidance

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

3. Creating a Master File

3.1 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 in addition to the sterility status of the API. Also, the compendial standard provided in any of the publications mentioned in Schedule B to the *Food and Drugs Act* should be included if it applies.

Consideration should be given to the following:

- 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 3.6 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 clearly state this and provide information to distinguish the different products in a side-by-side comparison table. The MF Holder should provide a MF name that distinguishes the MF from any previously registered MFs.

3.2 Format and Structure of the Master File

The VDD no longer accepts paper copies of MFs. MFs must follow the formatting requirements outlined in the Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format and the Notice: Validation rules for regulatory transactions provided to Health Canada in the "non-eCTD electronic-only" format.

Any current MFs that have not yet been converted into a non-eCTD electronic format will no longer be assessed and no updates and cross-references will be accepted. The MF will be suspended until the MF Holder submits a cover letter to the VDD along with the converted MF in electronic format, including any applicable updates, or with a declaration that there are no changes to the information provided to the VDD previously. The same MF number will be retained.

Refer to Appendix A and Appendix B of this document for the structure of information that should be followed in the Applicant Part and the Restricted Part for Type I and Type IV MFs.

3.3 Official Language of Correspondence

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

3.4 Letters of Access (LoA)

The MF will only be reviewed in conjunction with the assessment of the Applicant's veterinary drug submission.

The following information should be included in each LoA:

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

A sample LoA can be found in Appendix C.

3.4.1 Filing a Letter of Access (LoA)

A separate LoA is required for each Applicant who cross-references the MF in their veterinary drug submission. The LoA needs to be signed by the MF Holder or Authorized MF Agent on official company letterhead. It must include the assigned MF number. Therefore, MFs must be received in advance of the Applicant's filing of a drug submission with the VDD in order that the MF holder can provide the Applicant with a copy of the LoA with the assigned MF number. However, the MFs are not to be filed more than one year prior to the filing of a drug submission.

For Type I and IV MFs, a LoA is for a MF in its entirety and is valid for all related 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, 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 that is not included in the first LoA, a new LoA is required.

For MFs that reference other MFs, MF Holders or Authorized MF Agents are required to file a LoA granting another MF Holder access to their MF. When a MF Holder is filing a Type IV MF that references a Type I MF, the MF Holder for the Type I MF must file a 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.

LoAs should be revised and refiled when the Applicant's name has been changed. If the MF Holder is changing their 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.

3.5 Appointment of the Authorized Master File Agent

When an Agent is appointed by the MF Holder, an agent authorization letter from the MF Holder is required (see Appendix D). It should indicate who is being appointed and what they are responsible for, which includes but is not limited to the following:

- issuing LoAs
- handling deficiencies
- handling associated correspondence
- filing updates and administrative changes

When the MF Holder is not based in North America, it is recommended that a North American MF Agent, who is familiar with Canada's *Food and Drugs Act* and associated regulations, be used. An Authorized MF Agent may perform all functions listed in this guidance document after they have been appointed by the MF Holder to act on their behalf.

3.6 When to File a New Master File Registration

Each of the following examples is considered to be a situation where 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 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 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

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

If the API manufacturer or MF Holder has a current valid Certificate of Suitability (CEP), and they can provide all the attestations as per Health Canada's Guidance Document: Use of Certificates of Suitability as Supporting Information in Drug submissions (2017/08/21, Section 2.1.1), it is not necessary to submit the Restricted and Applicant Parts of the MF in the application. Only information in Appendix E of this document is required.

- If a CEP is not available at the time of filing of the MF, it could be provided as an update as soon as it becomes available. Revised CEPs will be accepted with or without simultaneous updates to the MF.
- CEPs and associated attestations outlined in Appendix E should be made available to the Applicant.
- Updates to CEPs and associated attestations should be made available to the Applicant. The CEP number should be stated in the attestations.

3.8 Additional Filing Information

MFs cannot be filed through Health Canada's Regulatory Enrolment Process (REP). Refer above to Section 3.2 Format and Structure of the MF.

Veterinary MFs may be filed with the VDD using content accepted by the United States Food and Drug Administration's (US FDA) Center for Veterinary Medicine (CVM). To facilitate review by the VDD, this should include a table of contents (or an index) mapping the US MF content to the Canadian MF content along with all required Canadian-specific information. Please use the structure presented in Appendix A and Appendix B of this document as the basis for your table of contents (or index). As the VDD no longer accepts paper copies of MFs, any such filing must be sent to the VDD in electronic format only as outlined in Section 3.2 above.

4. Making Changes to a Registered Master File

Updates are to be filed by the MF Holder or Authorized MF Agent. Updates 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: Post-Notice of Compliance (NOC) Changes – Quality Document.

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 the VDD as per the Guidance Document: Post-Notice of Compliance (NOC) Changes – Quality Document. MF Holders should ensure that all updates are filed prior to the Applicant submitting any post-NOC changes to the VDD.

4.1. Filing Requirements

An entire MF must not be filed with an update unless it is a conversion as outlined in the Guidance Document Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format.

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

- MF number
- Type of MF (I, II, III or IV)

Additional administrative documents:

- 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)
- up-to-date list of all Applicants authorized to access the MF
- MF Application Form, even if no changes have been made since last filing

To file an update to a MF (Type II and Type III MF) for an additional formulation or component:

- 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.

4.2 Administrative Changes

Administrative changes to a MF may be filed at any time throughout the life cycle of the MF.

4.2.1 Transfer of Ownership and Company Name Changes

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

- buyout
- 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) to include:
    - name and address of the new MF Holder
    - list of all affected MFs
    - confirmation that all LoAs remain valid
    - confirmation that all manufacturing sites and processing remain the same
    - confirmation that the previous Authorized MF Agent is still valid, if applicable

- 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 (e.g., proof of incorporation or certificate of continuance)

- up-to-date list of all Applicants authorized to access the MF

- revised MF Application Form

- side-by-side comparison table of the administrative changes (to be included in Module 1, Section 1.0.7 General Note to Reviewer)

4.2.2 Change to the Authorized Master File Agent

If a company wishes to change the current Authorized MF Agent, a letter should be provided in writing from the MF Holder to the VDD in the proper non-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 the VDD to provide duplicate information to a new appointee.

4.3 Withdrawal of Letters of Access

MF Holders who wish to withdraw a LoA for a particular Applicant to cross-reference a MF should advise the VDD in writing (in proper non-eCTD format) of the 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 cross-referenced in subsequent applications.

4.4 Master File Closures and Reactivations

In order to close a MF, the MF holder should:

- notify the VDD in the proper non-eCTD format, of the reason for the closure
- include 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 the VDD).

On closure, MF Holders should provide the VDD with a list of all Applicants using the MF. It is understood that when a 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 cross-referenced in subsequent Canadian drug submissions unless the CBI is submitted directly to the Applicant who will include the information in their drug submission.

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 a 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 relate to safety, the Applicant should be informed of the reasons and should contact Health Canada regarding the Health Risk Assessment and any recall actions. Health Canada will retain the MF 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.

If the MF Holder wishes to reactivate a MF that was closed but remains otherwise up-to-date (i.e., no changes have been made since closure), then the MF Holder must submit a cover letter requesting the reactivation and the application form. If changes were made, then the MF Holder must also provide the updated information under 1.0.7 Note to General Reviewer and the Modules 2 and 3.

If the MF was closed prior to being converted in electronic format, then an entire updated MF, along with a cover letter and application form, must be submitted.

5. Submitting the Master File

5.1 Where to Send Master File Registrations

A MF used for veterinary products only is to be submitted to the VDD. Contact the VDD about options to file electronically prior to filing (see below for Contact Information).

5.1.1 Shipping and Customs Information

Electronic filing options may be available. Please contact the VDD prior to filing.

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

5.2 Application and File Maintenance Requirements

All correspondence (e.g., cover letters, LoAs to a MF) should come from the MF Holder or Authorized MF Agent, where applicable. Any information filed by a third party will be rejected and destroyed as per Health Canada procedures.

The MF Holder should provide the most recent version of the MF to the Applicant filing the drug submission and referencing the MF.

5.3 Processing the Master File

When Health Canada receives a MF registration package, the following activities are performed:

- assigning a MF number to the MF (only for new MF registrations)

- verifying that the correct information, documents and forms have been filed in the correct format (refer to Section 3.2 Format and Structure of the MF), and that all submitted information, documents and forms are administratively complete

Once the MF registration package is administratively complete:

- a filing date is assigned (which is the date when the MF is considered administratively complete)

- an acknowledgement letter (with a MF number) is sent to the designated MF contact person (MF Holder or Authorized MF Agent) as listed on the MF Application Form

5.4 Communications with MF Holder During the Assessment of the MF

The Applicant will be notified if the veterinary drug submission is considered inadequate due to outstanding issues that need to be addressed with the MF. However, all communications with respect to the Restricted Part of the MF during the review of an Applicant's veterinary drug submission will be kept exclusively between the MF Holder (or Agent) and the VDD. Issues pertaining to the Applicant Part of the MF (e.g., analytical methods, stability data) will be communicated to the Applicant, but may also be forwarded to the MF Holder.

The following types of requests for information may be sent to the MF Holder (or Agent):

- Solicited data
- Clarification Request
    - email requesting clarification of information to be responded to within a short specified timeframe
- Letter of Deficiency
    - issued if MF Holder (or Agent) does not respond to the Clarification Request within the given timeframe
    - issued if there are a significant number of deficiencies

If additional time is required to respond to the VDD's request, then the MF Holder must inform the VDD either by contacting the Applicant for the associated submission who will then contact the VDD to request an extension, or by requesting an extension directly with the VDD, while notifying the Applicant. The VDD will grant extension to respond as deemed necessary.

If the response to the 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.

5.5 Performance Standards

The VDD will process all information and material filed in the MF registration within 20 calendar days of receiving an administratively complete package.

It may be necessary to place the transaction on Administrative Hold if the package is incomplete (e.g., missing required information or forms) or provided in the incorrect format.

Failure to respond to a request for additional or corrected information in the prescribed time will result in the MF transaction being destroyed as per Health Canada procedures. When the reason for the hold is satisfactorily addressed, the MF transaction will be considered administratively complete and a filing date will be applied.

5.6 Master File Fees

There are no fees for the filing of a MF, an update, or LoA that relate to a veterinary product only.

Contact Information

For questions or comments related to this guidance document and to MFs used for a veterinary product only, please contact:

Veterinary Drugs Directorate (VDD)
Health Products and Food Branch
Health Canada
Holland Cross Complex
14-11 Holland Avenue
Address Locator: 3000A
Ottawa, ON K1A 0K9
Email: HC.vdd.skmd.so-dgps.dmv.cp.SC@canada.ca
Telephone: 613-948-7615

For questions or comments related to MFs used for **both** veterinary and human products, please contact:

Bureau of Pharmaceutical Sciences (BPS)
Therapeutic Products Directorate
Health Products and Food Branch
Health Canada
Address Locator: 0201D
Ottawa, Ontario K1A 0K9
Email: hc.bps.enquiries.sc@canada.ca
Telephone: 613-941-3184
Fax: 613-941-0571

References

For related information, refer to the following documents:

- *Food and Drugs Act*
- *Food and Drug Regulations*
- *Access to Information Act*
- *Library and Archives of Canada Act*
- Forms – Applications and submissions – Veterinary drugs
- Guidance Documents – Legislation and guidelines – Veterinary drugs
- Guidance Documents – Applications and submissions – Drug products
- Guidance Document: Use of Certificates of Suitability as Supporting Information in Drug Submissions
- Compliance and Enforcement/Good Manufacturing Practices/Validation
- Chemical Entity Products/Quality
- VICH Guidelines Adopted by Canada
- VICH Guidelines

Appendices

Appendix A: MF Type I – Drug Substance – Structure (Template) and Distribution of MF Information Between the Applicant and Restricted Parts

Module/Folder Names		Applicant Part	Restricted Part
Module 1			
1.0	Correspondence		
1.0.1	Cover Letter	-	√
1.0.3	Copy of Health Canada issued Correspondence • Clarification Request • Letter of Deficiency • Screening Deficiency Notice (SDN)	-	√
1.0.4	Health Canada Solicited Information • Q&A Response to Clarification Request • Q&A Response to Letter of Deficiency	-	√
1.0.7	General Note to Reviewer	-	√
1.1	Table of Contents	-	√
1.2	Administrative Information		

1.2.1	Application Forms
	• MF Application/Amendment Form
	• Can include:
	  ○ Agent Appointment Letter
	  ○ Agent Withdrawal Letter
	  ○ Agent Name Change
		-	√

1.2.3	Certification and Attestation Forms • BSE/TSE Attestation Form • Certification of Suitability (CEP) • CEP – Update • CEP – Attestations • Statement of Commitment	√	√
1.2.5	Compliance & Site Information		
1.2.5.2	Establishment Licensing	-	√
1.2.5.5	Good Manufacturing Practices	-	√

	• Certificate of Compliance		
1.2.6	Authorization for Sharing Information • Letter of Access • Withdrawal of Authorization	-	√
1.2.7	International Information	-	√
Module 2: Common Technical Document Summary			
2.3	Quality Overall Summary	√(1)	√(1)
Module 3: Quality			
3.1	Table of Contents of Module 3	√	√
3.2	Body of Data		
3.2.S	Drug Substance		
3.2.S.1	General Information		
	Nomenclature	√	-
	Structure	√	-
	General Properties	√	-
3.2.S.2	Manufacture		
	Manufacturer(s)	√	-
	Description of Manufacturing Process and Process Controls	√(2)	√(3)
	Control of Materials	-	√
	Control of Critical Steps and Intermediates	√(4)	√(5)
	Process Validation and / or Evaluation	-	√
	Manufacturing Process Development	-	√
3.2.S.3	Characterisation		
	Elucidation and Structure and Other Characteristics	√	-
	Impurities	√	√(6)
3.2.S.4	Control of Drug Substance		
	Specification	√	-
	Analytical Procedures	√	-
	Validation of Analytical Procedures	√	-
	Batch Analyses	√	-

	Justification of Specification	√	√(7)
3.2.S.5	Reference Standards or Materials	√	-
3.2.S.6	Container Closure System	√	-
3.2.S.7	Stability		
	Stability Summary and Conclusions	√	-
	Post-approval Stability Protocol and Stability Commitment	√	-
	Stability Data	√	-
3.2.A	Appendices		
	Facilities and Equipment	-	√
	Adventitious Agents Safety Evaluation	-	√

("√" = Accepted / "-" = Not Applicable)

1. Only relevant sections of the VDD QOS should be completed.

2. A flow chart (including molecular structures and all reagents/solvents) and a short description can be sufficient, if additional detailed information is presented in the Restricted Part. However, for sterile drug substances full validation data on the sterilization process should be provided in the Applicant Part.

3. Provide detailed information.

4. If the information is also relevant for the Applicant.

5. The information is considered to be proprietary, and it will be held strictly confidential from the Applicant by Health Canada.

6. If the information relates to the detailed description of the manufacturing process and the MF Owner sufficiently justifies that there is no need to control these impurities in the final drug substance.

7. If the information relates to the detailed description of the manufacturing process, control of materials and process validation.

Appendix B: MF Type IV - Drug Products – Structure (Template) and Distribution of MF Information Between the Applicant and Restricted Parts

Module/Folder Names		Applicant Part	Restricted Part
Module 1			
1.0	Correspondence		
1.0.1	Cover Letter	-	√
1.0.3	Copy of Health Canada issued Correspondence • Clarification Request • Letter of Deficiency • Screening Deficiency Notice (SDN)	-	√
1.0.4	Health Canada Solicited Information • Q&A Response to Clarification Request • Q&A Response to Letter of Deficiency	-	√
1.0.7	General Note to Reviewer	-	√
1.1	Table of Contents	√	√
1.2	Administrative Information		
1.2.1	Application Forms • MF Application/Amendment Form • Can include ➢ Agent Appointment Letter ➢ Agent Withdrawal Letter ➢ Agent Name Change	-	√
1.2.3	Certification and Attestation Forms • BSE/TSE Attestation Form • Statement of Commitment	√	√
1.2.4	Compliance & Site information		
	Establishment Licensing	-	√
	Good Manufacturing Practices • Certificate of Compliance	-	√
	Authorization for Sharing Information • Letter of Access	-	√

	• Withdrawal of Authorization		
	International Information	-	√
Module 2: Common Technical Document Summary			
	Quality Overall Summary (QOS)	√(1)	√(1)
Module 3: Quality			
3.1	Table of Contents of Module 3	√	√
3.2	Body of Data		
3.2.P	Drug Product		
3.2.P.1	Description and Composition of the Drug Product*	√	√(3)
3.2.P.2	Pharmaceutical Development	√(4)	√(3)
3.2.P.2.1	Components of the Drug Product	√(5)	√
3.2.P.2.2	Drug Product*	-	√
	Manufacturing Process Development*	-	√
	Container Closure System*	-	√
	Microbiological Attributes*	-	√
	Compatibility*	-	√
3.2.P.3	Manufacture		
	Manufacturer(s)	√	√
	Batch Formula	√	√
	Description of Manufacturing Process and Process Controls	√(2)	√(3)
	Control of Critical Steps and Intermediates	√(4)	√(6)
	Process Validation and / or Evaluation	-	√
3.2.P.4	Control of Excipients	√	√
	Specifications	-	√
	Analytical Procedures	-	√
	Validation of Analytical Procedures	-	√
	Justification of Specification	-	√
	Excipients of Human or Animal Origin	-	√
	Novel Excipients	-	√
3.2.P.5	Control of Drug Product		

	Specifications	√	-
	Analytical Procedures	√	-
	Validation of Analytical Procedures	√	-
	Batch Analyses	√	-
	Characterisation of Impurities	√	√(7)
	Justification of Specifications	√	√(8)
3.2.P.6	Reference Standards or Materials	√	-
3.2.P.7	Container Closure System	√	-
3.2.P.8	Stability		
	Stability Summary and Conclusions	√	-
	Post-approval stability Protocol and Stability Commitment	√	-
	Stability Data	√	-
3.2.A	Appendices		
	Facilities and Equipment	-	√
	Adventitious Agents Safety Evaluation	-	√
	Excipients	-	√
3.2.R	Regional Information		
3.2.R.1	Production Documentation		
3.2.R.1.1	Executed Production Documents*	-	√
3.2.R.1.2	Master Production Documents*	-	√

("√" = Accepted / "-" = Not Applicable)

1. Only relevant sections of the VDD QOS should be completed.

2. A flow chart (including all manufacturing steps, excipients and processing agents) and a short description is sufficient, if additional detailed information is presented in the Restricted Part.

3. Provide detailed information.

4. If the information is also relevant for the Applicant.

5. Complete qualitative composition should be provided to the Applicant.

6. If this information is not relevant for the Applicant.

7. If the information relates to the detailed description of the manufacturing process and the MF Owner sufficiently justifies that there is no need to control these impurities in the final drug product.

8. If the information relates to the detailed description of the manufacturing process, control of materials and process validation.

Note: Text with an asterisk (*) refers to sections of MFs that are not defined in Appendix D of Health Canada's Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format.

Appendix C: Sample – Letter of Access

(Date)

Veterinary Drugs Directorate
Holland Cross Complex
14-11 Holland Avenue
Address Locator: 3000A
Ottawa, ON K1A 0K9

Dear Sir or Madam:

Subject: Letter of Access – (Master File Name) MF # (fYYYY9XX) (or New Master File if a New Submission)

Please accept this letter as authorization for Health Canada to review (Master File Name, MF # fYYYY9XX) referenced by:

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

In support of their drug submissions, filed with the Veterinary Drugs Directorate of the Health Products and Food Branch.

Yours sincerely,

(Signature)

Appendix D: Sample – Agent Authorization

(Date)

Veterinary Drugs Directorate
Holland Cross Complex
14-11 Holland Avenue
Address Locator: 3000A
Ottawa, ON K1A 0K9

Dear Sir or Madam:

Subject: Master File Agent Authorization – (Master File Name) MF # (fYYYY9XX)

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 associated correspondence

d) filing updates and administrative changes

Yours sincerely,

(Signature)

Appendix E: Sample – CEP Attestation Letter

(Date)

Veterinary Drugs Directorate
Holland Cross Complex
14-11 Holland Avenue
Address Locator: 3000A
Ottawa, ON K1A 0K9

Dear Sir or Madam:

Subject: Drug Substance – CEP # XXXXXXXXXXXXXX

On behalf of [insert name of API Manufacturer Name/MF Holder], I [insert name of person who is attesting the document], 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. Also, 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.

Yours sincerely,

(Signature of person who is attesting the document)