**OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER**

# VETERINARY MASTER FILES WITH MANUFACTURING INFORMATION



## I. PURPOSE

This document discusses the types of manufacturing master files, information to be reviewed, procedures governing the review of master files, and Center for Veterinary Medicine (CVM) expectations for the manufacturing master file holder.

A master file (MF) is a submission to the Food and Drug Administration (FDA) prepared by a pharmaceutical manufacturer that may be used to provide confidential, detailed information. There is no regulatory requirement to file a master file. A master file may be submitted so that other sponsors can reference the information to support their applications without having access to the information themselves. Alternatively, a firm may submit information in a master file so that they can submit the information to one file for review but reference that information in multiple other applications or files. For manufacturing master files, the contents can include facilities, processes, or articles used in the manufacturing, processing, packaging, and stability of one or more veterinary drugs. We generally refer to MFs on file with the CVM as Veterinary MFs (VMFs). Those on file with the Center for Drug Evaluation and Research (CDER) are referred to as Drug MFs (DMFs). There are no essential content differences between DMFs and VMFs for manufacturing purposes other than their filing location, formatting requirements, and numbering systems. The Center for Biologics Evaluation and Research (CBER) also has DMFs, but it's less clear what differences there might be between the DMFs held by CBER and VMFs.

A MF is NOT a substitute for an investigational new animal drug (INAD), generic investigational new animal drug (JINAD), new animal drug application (NADA), abbreviated new animal drug application (ANADA), or conditional new animal drug application (CNADA). The information contained in a MF may be used to support an INAD, JINAD, NADA, ANADA, CNADA, another MF, or amendments or supplements to any of these. The MF is not approved or disapproved, but rather it is found adequate or deficient to support of a referencing submission.

## II. BACKGROUND

There are different types of master files including public master files (PMFs), veterinary master files (VMFs), and drug master files (DMFs).

Public master files (PMFs) contain information that is available to the public without the concern for trade secret and confidentiality associated with other types of master files (i.e., VMFs and DMFs). Often these files contain safety and effectiveness information generated by researchers in other government agencies or academia that has been made possible with public funds. These data may be used to support new animal drug approvals. See https://www.fda.gov/animal-veterinary/minor-useminor-species/public-master-files-pmfs-supporting-applications-minor-use-and-minor-species-drugs for more information about PMFs. These are outside the scope of this document as the process for these differs from that of VMFs.

VMFs are held at CVM and contain information that can be used to reference information to support new animal drug approvals. This P&P applies specifically to manufacturing VMFs. There are several classifications of VMFs which are based on the type of information submitted to that VMF. The categories of VMFs are:

- Type II:[1] Manufacturing Information for Drug Substances and Intermediates
- Type III: Packaging Material
- Type IV: Excipient, Colorant, Flavor, Essence or Material Used in their Preparation
- Type V: FDA Accepted Reference Information
- Type VI: Free-Choice Medicated Feeds and Medicated Feed Assay Methods
- Type VII: Division of Animal Bioengineering and Cellular Therapies (DABCT) project information and Tech Team Working Process[2] and are not manufacturing VMFs
- Type VIII: Import Tolerance Requests[3] which will be reviewed by ONADE's Division of Human Food Safety and Environmental Safety Team with the Office of Surveillance and Compliance (OSC) and are not manufacturing VMFs

Emergency Use Authorization may be included in a VMF, but will be handled outside the scope of this document.

DMFs are held by CDER and can be used to reference information to support both human and animal applications. DMFs only have Types II, III, IV and V. The information in these types of master files are equivalent between DMFs and VMFs. Where a DMF has already been reviewed by a CDER reviewer, CVM will accept the outcome of the review unless there are animal specific concerns. Note that VMFs can

[1] Type I VMFs are no longer accepted by CVM. Previously they were allowed for facility information, which is now included in either the Type II or V VMFs.
[2] See ONADE SOP 1243.153.001 Tech Team Process
[3] See (https://www.fda.gov/animal-veterinary/import-exports/import-tolerances) for more information on Import Tolerance Requests

only be used to support animal products or, rarely, DMFs (which may then be used for human products) but not human products directly.

## III. VMF TYPES AND THEIR CONTENTS

### A. Type II: Manufacturing Information for Drug Substances and Intermediates

A Type II VMF contains manufacturing information for bulk drug substances or intermediates used in the further manufacture of a bulk drug substance. These VMFs should be limited to a single drug intermediate or drug substance. This information may include general information on the molecule, information on the manufacturing facility, details of the manufacturing process used, and controls such as release and stability tests and methods.

Additional guidance for the type of information found in a Type II VMF is available in CVM Guidance's for Industry (GFI) #57: Preparation and Submission of Veterinary Master Files, GFI #169: Drug Substance Chemistry, Manufacturing, and Controls Information, GFI #216: Chemistry, Manufacturing, and Controls (CMC) Information - Fermentation-Derived Intermediates, Drug Substances, and Related Drug Products for Veterinary Medicinal Use, and GFI #5: Drug Stability Guidelines. This is not an exhaustive list.

### B. Type III: Packaging Material

This type of VMF could contain information about the intended use, components, composition, and controls of a packaging material, information about the suppliers/fabricators of the components, and data supporting acceptability of the packaging material for its intended use. Such data may include evidence of compliance with USP <661> or <660> and 21 CFR Parts 175 through 178, Indirect Food Additives.

### C. Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation

Identification and characterization data, such as method of manufacture, release specifications, and testing methods may be submitted in a Type IV VMF for materials intended for use in veterinary pharmaceuticals but not intended to be active ingredients. Toxicological data for these substances may be included under this type of VMF if the data are not otherwise available by cross-reference to another document.

A Type IV VMF should include any other supporting information and data that are not available by cross reference to another document. Usually, the official compendia for excipients and Code of Federal Regulations (CFR) FDA regulations for color additives (21 CFR Parts 70 through 82), direct food additives (21 CFR Parts 170 through 173), indirect food additives (21 CFR Parts 174 through 178), and food substances (21 CFR Parts 181 through 186) are sufficient as sources for non-proprietary information. CVM may recommend that a potential Type IV VMF holder not submit a VMF if sources such as those above meet the needs of the firm.

### D. Type V: FDA Accepted Reference Information

This type of VMF may include reference information that is not covered by Type II through Type IV VMFs. Some examples of these types of information may include:

- Non-product-specific procedures and sterilization process validation information from contract manufacturers of aseptically processed sterile finished drug products and contract firms engaged in terminal sterilization of finished products (e.g., ethylene oxide, gamma radiation) to support a claim of sterility.

  For additional guidance on the content and format of such information, see CVM GFI #48: Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products and FDA GFI Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes.

- Manufacturing procedures and controls for finished dosage forms or medicated articles.

  CVM does not recommend that drug product information be submitted in a VMF. Such information should ordinarily be submitted in an INAD, JINAD, NADA, ANADA, or CNADA. However, if this information cannot be submitted in an INAD, JINAD, NADA, ANADA, or CNADA, it should be submitted in a Type V VMF. When a Type V VMF is submitted for a drug product or medicated article, the applicant/holder should follow 21 CFR 514.1(b)(4) and (5).

- Environmental safety studies not appropriate for submission to another VMF type.

- Animal effectiveness, safety, residue chemistry and metabolism, or toxicity information.

  This type of information is typically contained in an INAD or NADA for a specific product under investigation. However, in instances where the information and data may be applicable to more than one animal drug application, it may be advantageous to maintain the information in this type of VMF. CVM does not recommend also including manufacturing information in the same VMF.

- Information and supporting data that is not covered by a Type II through IV or Type VI VMF.

CVM discourages the use of Type V VMFs for miscellaneous information, duplicate information, or information that should be included in one of the other types of VMFs. If any holder wishes to submit such information to a Type V VMF, they should first contact the appropriate division at CVM, to discuss the proposed submission.

### E. Type VI: Free-Choice Medicated Feeds and Medicated Feed Assay Methods

Type VI VMFs contain information related to medicated feeds. Examples of content include:

- Feed assay methods, including Official Methods of Analysis of Association of Official Agricultural Chemists (AOAC) International, with validation and collaborative study procedures and data.
- Free-choice medicated feed product manufacturing information as required in 21 CFR 510.455, including formulations, manufacturing procedures, analytical controls, labeling, stability data, and manufacturing site information.
- Effectiveness/consumption data for a free-choice feed as described in GFI #13: Evaluation of Effectiveness of New Animal Drugs for Use in Free-Choice Feeds-Medicated Block.

Additional guidance related to information that may be provided in a Type VI VMF is available in CVM GFI #23: Medicated Free Choice Feeds--Manufacturing Control, GFI #135: Validation of Analytical Procedures for Type C Medicated Feeds, GFI #136: Protocols for the Conduct of Method Transfer Studies for Type C Medicated Feed Assay Methods, and GFI #137: Analytical Methods Description for Type C Medicated Feed

## IV. COMMUNICATIONS REGARDING VMFS

### A. Meetings with VMF Holders or U.S. Agents

Meetings may be requested related to material submitted to a master file. If the party requesting the meeting is the master file holder and/or U.S. agent, the meeting request should be made to the specific VMF. If the party requesting the meeting is the drug product manufacturer, the meeting request should be made to the referencing submission (see C below).

### B. Communications with VMF Holders or U.S. Agents

Where a U.S. agent has been identified, all communication should be with that U.S. agent. This includes both formal communication such as letters, as well as informal communication such as phone calls and emails. The firm may request in the VMF that correspondence be issued directly to them instead of the U.S. agent, and in that case, we would use the contact person identified by the firm for all correspondence.

CVM typically does not inform the VMF holder/U.S. agent that a VMF amendment is adequate to support an application, but CVM may state whether the amendment is complete or incomplete if asked by the VMF holder or U.S. agent.

### C. Communication with Sponsors with Referencing Submissions

If the drug product manufacturer requests a meeting under the context of how the referencing submission should address some topic related to the drug substance, no propriety information from the VMF may be shared with the drug product

manufacturer. Comments such as that the VMF is incomplete/deficient to support their application or the GMP status of the VMF facility is unacceptable or pending are appropriate. The reasons that the VMF is deficient or the GMP status is unacceptable may not be shared.

## V. CVM EXPECTATIONS FOR THE VMF HOLDER

Reviewers of VMFs should assure that:

- The VMF holder has provided a Letter of Authorization (LOA) to the drug sponsor when reference is to be authorized. A current list of authorized users should be maintained in the VMF, typically as part of an annual report.
- If the VMF has significant changes, all referencing applications should submit a supplement referencing those changes to the master file. Before making significant changes in processes covered in the VMF, the holder should notify each sponsor authorized to reference the file. If an animal drug sponsor has used VMF information to support an (A)NADA approval, the sponsor is obligated to supplement or amend the affected application(s).
- If the VMF holder changes the U.S. agent, then the holder provides a letter explaining the change and may appoint a new agent. Note that foreign facilities are required to have a U.S. agent to allow scheduling of inspections but VMFs are not required to have a U.S. agent for the purposes of correspondence to the file, although they typically do if they are foreign.[4]

## VI. HOW TO REVIEW A VMF

VMFs may be submitted at any time, but are not initially reviewed until the VMF is referenced by an (A)NADA, (J)INAD, or CNADA. Once the VMF has been referenced, it is generally reviewed with the same due date as the referencing submission.

1. Assure that at least one new animal drug submission or application (NADA, ANADA, INAD, JINAD, CNADA, or other master file) references the VMF.

   STARS list due dates for VMFs as 180 days, but this does not reflect an accurate depiction of the statutory time frames for these submissions. The due date(s) of the referencing submission(s) should be noted to allow a more accurate picture of when a VMF should be closed out in Appian.

   - Each referencing drug application should have an attached Letter of Authorization (LOA). See CDER's guidelines and template for LOAs here: https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs. The LOA for a VMF should contain:
     - Date of letter
     - Name of VMF holder
     - VMF number
     - Name of persons authorized to incorporate information in the MF by reference.

[4] See P&P 1243.2020

- Specific products covered by the VMF
- Sections, volumes and page numbers to be referenced
- Statement of commitment that the VMF is current and that the holder will abide by the statements made in it.
- Signature of the authorizing official/agent
- Typed name and title of the official authorizing reference to the file.

- Assure that the VMF contains either a copy of the same LOA as above or a current list of sponsors authorized to reference the file that includes the sponsor(s) for the referencing submission(s). If one of these criteria are not met, discuss with your team leader what steps to follow. Options include:

  - Not reviewing the VMF.
  - Asking the sponsor to obtain a LOA and submit it as an amendment to the application, and request that the VMF holder submit a copy of the LOA to the VMF.
  - Contacting the VMF holder and determining whether the applicant is authorized to reference the file, and having the holder submit the LOA or a list of authorized users to the file.

2. Find the list of submissions to the VMF in STARS and have the submissions which have not yet been closed out in Appian assigned to the reviewer using your division's process.

   The reviewer should review all unreviewed VMF submissions with a correspondence date before the date of the referencing submission to support the referencing application. This may include submissions that were closed with the final action code Filed No Reply (FNR) because there was no referencing submission at that time; in this case the reviewer should open a Q submission for the review. If a VMF submission is received more than 10 days after the referencing submission was submitted, the reviewer should check with their team leader to determine if the submission should be included in the current review.

3. Decide if the VMF requires a consulting review[5]

   The consult may be created under either the VMF or the refencing submission and depends on the situation. Consult the team leader if you are unsure which submission to create the consult under.

4. Perform a quick check to see whether the VMF is grossly deficient.

   If information filed in the master file is grossly deficient, the referencing submission is subject to the refuse to file or refuse to review procedure.[6] Consult your team leader before taking this action.

5. Locate and skim through previous VMF review in CDMS for background information, as necessary

[5] See 1243.3200
[6] See 1243.2050

6. Evaluate the material in the relevant unreviewed VMF submissions (both open and closed) to determine whether it adequately supports the referencing application

   If there are any open submissions, the most recent will be used for the review and the other submissions will be closed using the final action code FNR. If all of the relevant unreviewed VMF submissions have already been closed, a Q submission will be opened for the review.

7. Document deficiency comments revealed during the VMF review process

   If there are deficiency comments that warrant an incomplete MF comment in the referencing submission(s) or would require not approving the referencing submission(s), the master file will be found deficient. These comments should ask for information that would affect drug product quality.

   If there are comments that do not warrant an incomplete MF comment in the referencing submission(s) and should not hold up approval of the referencing submission(s), the reviewer should issue an Information Request letter. These are typically comments that would not affect drug product quality. The Review Summary field should be updated to indicate if an Information Request letter was sent, since the same final action code is used to send both incomplete and information request letters.

8. Draft a letter to master file holder or U.S. agent for reviews that are incomplete or require information request

   The appropriate contact person can be determined from the file. If a U.S. agent is appointed for the VMF, check the master file to determine if the agent may receive all correspondence pertaining to the master file. If this information is not complete, then contact the U.S. agent or master file holder, as appropriate, and identify responsible parties pertaining to correspondence with FDA. If there are multiple U.S. agents identified, contact the master file holder to decide the appropriate contact person for correspondence prior to issuing the letter. Foreign master file holders may request that correspondence be sent directly to a contact person at the firm.

   Final the review and letter as described in Sections VIII and IX below.

9. Inform reviewer of referencing submissions of the status of the VMF

   The reviewer of the refencing submission may also review the master file, or different reviewers may be reviewing each. When different reviewers are working on related submissions, communication is critical

## VII. FINAL ACTION CODES FOR A VMF

The information within the VMF is intended to support a referencing submission. Master files are not approved, and if the information in the VMF is adequate to support the referencing submission, no correspondence is sent to the VMF holder. They may be found deficient/incomplete if additional clarification or information is required to determine whether the information provided is sufficient to support the referencing submission. The final action codes used will vary depending on the type of

master file submission. Below are final actions that may apply; this is not an exhaustive list.

| Final action | STARS Abbreviation | Code |
|---|---|---|
| Filed No Reply | FNR | 007 |
| Filed No Reply with Memo | FNR/MEMO | 009 |
| Incomplete Master File* | INCMPLT MF | 206 |
| Acknowledgment** | ACK | 033 |
| Closed Own | CLOSED OWN | 204 |
| Closed Agency | CLOSED AGY | 205 |
| Protocol concurrence | PROT CONCR | 045 |
| Protocol non-concurrence | PROT NCONC | 046 |

*This final action code is used for sending both Deficiency letters and Information Request (IR) letters. Because there is not currently a separate final action code for IR is not available, reviewers are asked to designate in the Review summary field that an IR letter was issued.

**The final action code ACK should be used for Q submissions, even if the submission is an incomplete or information request letter is being sent; the final action code INCPLT MF is not allowed for a Q submission type.

## VIII. CLOSING A VMF

### A. Holder Initiated

A holder who wishes to close a VMF should submit a request in eSubmitter as a CMC general correspondence (G). The cover letter from the holder should include a statement that the holder's obligations have been fulfilled and a list of notified users. One critical obligation is to ensure all lots placed on stability have completed stability data through the expiry/retest date. If the facility is closing an is no longer able to complete stability testing, they may propose an alternate laboratory to complete the remaining stability tests for the lots on stability.

A reviewer is assigned to the G submission containing the request to close the VMF. The reviewer should ensure complete stability data for all lots that have been placed on stability is provided in the file. It may also be appropriate to discuss with reviewers of applications that have referenced the VMF previously to ensure there are no changes that have been reported to referencing applications but not in the VMF itself yet. If more VMF information is required, CVM should recommend to the master file holder that the file remain open until the holder's obligations have been fulfilled.

### B. Agency Initiated

CVM may initiate closure of a VMF that is not being maintained through submission of annual reports or not reporting authorized users. The holder will be notified of CVM's intent to close the VMF.

### C. Final Action Package

The final action package consists of a or closure of a letter only. The letter should be written using the applicable VMF closure template. A review is not prepared for the closure of a VMF.

## IX. ASSEMBLING AND ROUTING THE FINAL ACTION PACKAGE FOR FINAL CLEARANCE

The final approval package generally consists of a review and/or letter. Build the sign-off in Appian according to the longest chain needed for your package. As described above, the actual documents and signatures required for each package may vary.

The reviewer and appropriate team leader sign both the review, if present, and the letter, if present.

When including documents in Appian, select Yes to answer the question "Should file be sent to the firm?" for only the letter.

## X. FINALING VMF SUBMISSIONS

If the submission is made electronically, we will close it out in Appian. If the submission is received in paper, reviewers will process the final action in Appian and the Records and Information Management Team will follow the process described in P&P 1243.3002 to send our response to the sponsor or outside party that made the submission.

## XI. REFERENCES

Code of Federal Regulations (Title 21)

Part 514.11, Confidentiality of data and information in a new animal drug application file.

Part 314.420(d), Drug master files.

Part 510.455, Requirements for free-choice medicated feeds.

Guidance for Industry

#13: Evaluation of Effectiveness of New Animal Drugs for Use in Free-Choice Feeds-Medicated Block

#23: Medicated Free Choice Feeds--Manufacturing Control

#48: Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products

#57: Preparation and Submission of Veterinary Master Files

#135: Validation of Analytical Procedures for Type C Medicated Feeds

#136: Protocols for the Conduct of Method Transfer Studies for Type C Medicated Feed Assay Methods

#137: Analytical Methods Description for Type C Medicated Feeds

CDER GFI Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes

#5: Drug Stability Guidelines

#169: Drug Substance Chemistry, Manufacturing, and Controls Information

#216: Chemistry, Manufacturing, and Controls (CMC) Information - Fermentation-Derived Intermediates, Drug Substances, and Related Drug Products for Veterinary Medicinal Use

CVM Program Policies and Procedure Manual - ONADE Reviewer's Chapter

1243.2020 – United States (U.S.)-Based Employee and U.S. Agent Representation of Foreign Sponsors

1243.2050 - Refuse to File and Refuse to Review

1243.3002 - Handling and Rejecting Paper Applications and Submissions

1243.3200 - Routing a Request to Obtain a Consulting Review of a Submission Tracking and Reporting System (STARS) Submission

ONADE Standard Operating Procedures and Scientific Reference Documents

1243.126.001 Tech Team Process

Import Tolerance Request information:
https://www.fda.gov/animal-veterinary/import-exports/import-tolerances

PMF information:
https://www.fda.gov/animal-veterinary/minor-useminor-species/public-master-files-pmfs-supporting-applications-minor-use-and-minor-species-drugs

CDER guidelines and templates for LOAs:
https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs

## XII. VERSION HISTORY

June 3, 2019 – Original version.

July 19, 2019 - Updated FDA.gov URL links to new directed links due to migration of new FDA.gov Website. No other updates needed.

August 14, 2019 – Revised because P&P 1243.3400 was converted to an ONADE SOP. All references to it were changed to reference the new SOP.

June 2, 2021 – Quality system review was completed, and no substantive edits were necessary. Minor edits were made to references and formatting.

November 11, 2021 – Updated the SOP number referenced in footnote 2 to new number 1243.153.001 Tech Team Process.

December 22, 2021 – References to P&P 1243.2020 United States (U.S.)-Based Employee and U.S. Agent Representation of Foreign Sponsors added to this document.