OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

VETERINARY MASTER FILES WITH MANUFACTURING INFORMATION

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I. PURPOSE

This document discusses the types of manufacturing master files (MFs), information to be reviewed, procedures governing the review of MFs, and CVM's expectations for the manufacturing MF holder.

A MF is a submission to FDA prepared by a pharmaceutical manufacturer that may be used to provide confidential, detailed information. There is no regulatory requirement to file a MF. A MF 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 MF so that they can submit the information to one file for review but reference that information in multiple other applications or files. For manufacturing MFs, 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 master files (VMFs). Those on file with the Center for Drug Evaluation and Research (CDER) are referred to as drug master files (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 a (generic) investigational new animal drug [(J)INAD] file, (abbreviated) new animal drug application [(A)NADA], or conditional new animal drug application (CNADA). The information contained in a MF may be used to support a (J)INAD, (A)NADA, 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 MFs including public master files (PMFs), veterinary master files (VMFs), and drug master files (DMFs).

PMFs contain information that is available to the public without the concern for trade secret and confidentiality associated with other types of MFs (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: primarily used by the Division of Animal Bioengineering and Cellular Therapies (DABCT) and are not manufacturing VMFs; and
- Type VIII: Import tolerance requests,[2] which are 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 MFs are equivalent between DMFs and VMFs. When a DMF has already been reviewed by a CDER reviewer, CVM accepts the outcome of the review unless there are animal-specific concerns. Note that VMFs can 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

Type II VMFs may contain 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

[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 https://www.fda.gov/animal-veterinary/import-exports/import-tolerances for more information on Import Tolerance Requests

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

Type III VMFs may contain information about the intended use, components, composition, and controls of a packaging material; information about the component suppliers/fabricators; and data supporting acceptability of the packaging material for its intended use. Such data may include evidence of compliance with USP <660> or <661> and 21 Code of Federal Regulations (CFR) Parts 175 - 178.

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

Type IV MFs may contain identification and characterization data, such as method of manufacture, release specifications, and testing methods 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 includes any other supporting information and data not available by cross-reference to another document. Usually, the official compendia for excipients and CFR FDA regulations for color additives (21 CFR Parts 70 - 82), direct food additives (21 CFR Parts 170 - 173), indirect food additives (21 CFR Parts 174 - 178), and food substances (21 CFR Parts 181 - 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, such as:

- 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;
- 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 (J)INAD, (A)NADA, or CNADA. However, if this information cannot be submitted in one of those file types, 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;
- animal effectiveness, safety, residue chemistry and metabolism, or toxicity information. This information is typically contained in an INAD or NADA for a specific product under investigation. However, in instances where the data and information may apply to more than one file or application, it may be advantageous to maintain the information in this type of VMF. CVM does not recommend including manufacturing information in the same VMF; and
- information and supporting data not covered by Types II-IV or a Type VI VMF.

CVM discourages the use of Type V VMFs for miscellaneous or duplicate information or information that should be included in another VMF. If a 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, such as:

- 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; and
- effectiveness/consumption data for a free-choice feed as described in GFI #13.

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 to discuss material submitted to a MF. If the meeting requestor is the MF holder or U.S. agent, the meeting request is made to the VMF. If the meeting requestor is the drug product manufacturer, the meeting request is made to the referencing submission (see Section C).

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

If a U.S. agent has been identified, then 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; if so, we 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 a 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 MF. 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, then the sponsor is obligated to supplement or amend the affected application(s); and
- 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 (see P&P 1243.2020).

VI. HOW TO REVIEW A VMF

A. Traditional Review

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

1. Ensure that at least one new animal drug submission or application [(A)NADA, (J)INAD, CNADA, or other MF] references the VMF. STARS lists the due dates for VMFs as 180 days, but this is not an accurate depiction of the statutory timeframes 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 include an LOA. See CDER's guidelines and template for LOAs here: https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs. The VMF LOA should contain:
  - date of letter,
  - name of VMF holder,
  - VMF number,
  - name of persons authorized to incorporate information in the MF by reference,
  - 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, and
  - typed name and title of the official authorizing reference to the file.
- Ensure 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, consult with your team leader (TL). Options include:
  - not reviewing the VMF;
  - asking the sponsor to obtain a LOA, submit it as an amendment to their application, and request that the VMF holder submit a copy of the LOA to the VMF; and
  - 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 VMF submission list in STARS and have the submissions that are not yet closed out in Appian assigned to the reviewer using your division's process. The reviewer reviews 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 opens a Q submission for the review. If a VMF submission is received more than 10 days after the referencing submission was submitted, the reviewer checks with their TL to determine if the submission should be included in the current review.

3. Decide if the VMF requires a consulting review per P&P 1243.3200. The consult may be created under either the VMF or the refencing submission and depends on the situation. Consult your TL 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 MF is grossly deficient, the referencing submission is subject to the refuse to file or refuse to review procedure per P&P 1243.2050. Consult your TL before taking this action.

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

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 is used for the review and the other submissions are closed using the final action code FNR. If all of the relevant unreviewed VMF submissions have already been closed, a Q submission is 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 MF is 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 issues 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 MF holder or U.S. agent, as appropriate, 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 MF to determine if the agent may receive all correspondence pertaining to the MF. If there are multiple U.S. agents identified, contact the MF holder to determine the appropriate contact person for correspondence prior to issuing the letter. Foreign MF holders may request that correspondence be sent directly to a contact person at the firm.

   If this information is not complete, then contact the U.S. agent or MF holder and identify responsible parties pertaining to correspondence with FDA. Final the review and letter as described in Sections VIII and IX.

9. Inform the reviewer of referencing submissions of the VMF status. The reviewer of the refencing submission may also review the MF, or different reviewers may be reviewing each. When different reviewers are working on related submissions, communication is critical.

B. Proactive Review of Type II VMFs

To enhance CVM's oversight on the drug supply chain and attempt to address drug substance manufacturing issues before they impact the supply of approved drugs, a proactive review process for Type II VMFs was initiated. Type II VMFs referenced in

the two most recent annual reports for a single (A)NADA qualify for proactive review and are included on the proactive VMF list. Once included on the proactive VMF list, incoming submissions with annual reportable changes to a VMF, which are maintained according to GFI #57 and submitted via CVM eSubmitter, are assigned and reviewed without waiting for a referencing submission. VMF submissions containing moderate or major changes (per GFI #83) do not qualify for proactive review and are only reviewed upon receipt of a referencing submission. The goal due date for the proactive review process is 180 days after CVM has received the submission.

VII. FINAL ACTION CODES FOR A VMF

The information in a VMF is intended to support the referencing submission. MFs are not approved. If the information in the VMF is adequate to support the referencing submission, no correspondence is sent to the VMF holder. VMFs 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 vary depending on the type of MF 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. Currently, there is no available final action code for IR, so reviewers designate in the Review Summary field that an IR letter was issued.

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

VIII. CLOSING A VMF

A. Holder Initiated

A holder who wishes to close a VMF submits 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 and 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 closure request. The reviewer ensures complete stability data for all lots placed on stability is provided in the file. It may also be appropriate to discuss with reviewers of applications that have previously referenced the VMF 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 recommends to the MF 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 is notified of CVM's intent to close the VMF.

C. Final Action Package

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

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 TL 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. CLOSING OUT VMF SUBMISSIONS

If the submission is made electronically, we close it out in Appian. If the submission is received in paper, reviewers process the final action in Appian. The Records and Information Management Team follows 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 (GFI)

#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

#83: Chemistry, Manufacturing and Controls Changes to an Approved NADA or ANADA

#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

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.

March 7, 2022 – Added proactive review of Type II VMFs to Section VI.

July 22, 2022 – Quality systems review for minor formatting updates.

May 18, 2023 – Revised to remove reference to the Tech Team process information as that SOP has been archived. To bring all office quality system documentation into compliance with the FDA Visual Identity Program approved fonts, ONADE has adopted Arial 11-point font. The font of this document was changed from Verdana 10-point font to Arial 11-point font.