Cross-Center Master Files: Where to Submit

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)
Office of Combination Products (OCP)

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I. INTRODUCTION

The purpose of this guidance is to provide recommendations to industry, specifically ***master file holders***,[1] regarding where (i.e., to which FDA center) to submit a ***master file*** (MF):[2, 3] (1) that is referenced in and intended to support more than one ***regulatory submission*** for which the ***lead center*** (i.e., the center that has primary review responsibility[4]) for those submissions may vary, or (2) where the information in the MF may need to be accessed and reviewed by more than one FDA center to support review of the ***referencing submission(s)*** (e.g., MFs referenced by ***combination product*** submissions). When an MF would be accessed by more than one center, it is referred to as a ***cross-center MF***. These recommendations are intended to help MF holders determine to which center to submit their MF. In turn, this may help MF holders identify any center-specific MF submission recommendations applicable to their situation.

Although the general MF concept is similar across the four medical product centers, the recommendations for submitting MFs and the MFs hosted by (i.e., located in) each center have aspects unique to that center (e.g., how to submit, content, format, naming convention, storage system). The recommended ***hosting center*** for specific MFs is based on the applications and files the MF is intended to support. This guidance does not provide information about the center-specific recommendations or FDA's MF review processes. Center-specific information can be found on FDA's website.[5]

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[1] Words and phrases in ***bold italics*** are defined in the Glossary.

[2] This document will generally use the inclusive term *master file* (MF) and will make distinctions between different center terminology and MF types as applicable (e.g., Drug Master Files (DMFs), Master Files for Devices (MAFs), Veterinary Master Files (VMFs)).

[3] Separate from the inclusive term *master file* used in footnote 2, FDA may, in accordance with section 565B of the Federal Food, Drug, & Cosmetic (FD&C) Act, identify an MF as a ***medical countermeasure (MCM) MF***. FDA's identification of an MCM MF does not change the center-specific MF submission type or process for any regulatory purpose. FDA will notify holders of MFs identified as MCM MFs in accordance with section 565B(d) of the FD&C Act.

[4] For purposes of this guidance, the lead center for a regulatory submission for a combination product is indicated by the terms *CBER-led*, *CDER-led*, and *CDRH-led*.

[5] For center-specific MF information, see CBER-specific information at https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/master-files-cber-regulated-products, CDER-specific information at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs, CDRH-specific information at

The recommendations in this draft guidance apply to MFs submitted to the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and Center for Veterinary Medicine (CVM) that are intended to be referenced by regulatory submissions for human and animal medical products. CVM Veterinary Master File (VMF) Types VI, VII, and VIII and their Public Master Files (PMFs) are not within the scope of the guidance. MFs submitted to the Human Foods Program or Center for Tobacco Products are not within the scope of the guidance.

FDA generally discourages MF holders from resubmitting previously submitted MFs that do not reflect the recommendations in this draft guidance. The recommendations provided, once finalized, are for new MF submissions going forward.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

MFs are voluntary submissions to FDA used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more FDA-regulated biological products, drugs, devices,[6] or combination products.[7] MFs can contain other types of information as well (e.g., nonclinical evaluations such as toxicology information, shared system REMS (risk evaluation and mitigation strategy)).

Typically, through a ***letter of authorization (LOA)***, MF holders can permit FDA to review the MF and permit one or more ***authorized parties*** (e.g., users including sponsors, applicants, or other MF holders) to incorporate by reference all or part of the MF's contents to support regulatory submissions to FDA without disclosing proprietary, confidential contents to those authorized parties. MFs are submitted solely at the discretion of their holders and are not required by statute or regulation. FDA does not approve or refuse to approve MFs. Instead, FDA reviews the technical contents of the MFs in connection with the review of the referencing

https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/device-master-files and the FDA guidance *Part III – Guidance on Scientific and Technical Information* (June 1987), and CVM-specific information at https://www.fda.gov/animal-veterinary/development-approval-process/veterinary-master-files. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] See section 201(h)(1) of the FD&C Act (21 U.S.C. 321(h)(1)) for the definition of *device*, section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)) for the definition of *drug*, and section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)) for the definition of *biological product*.

[7] Combination products are submitted to CBER, CDER, and CDRH. The term *combination product* does not include products regulated by CVM.

submission.[8] MFs can be used to support (but are not substitutes for) regulatory submissions reviewed by CBER, CDER, CDRH, and CVM. The review of an MF is typically triggered upon receipt of a referencing submission.

In certain instances, an MF might not be hosted by the center that receives the referencing submission. FDA generally discourages the submission of duplicate MFs to multiple centers, including convenience copies, to maintain appropriate version control within the Agency, among other things. Once an MF has been submitted to FDA, all centers can access and use the MF when it is referenced by regulatory submissions, regardless of which center is hosting the MF.

An MF is considered "cross-center" if it would be accessed and reviewed by FDA staff from more than one center. MFs can be used to support more than one referencing submission across multiple lead centers. Additionally, when reviewing an MF, the lead center can request expertise from another center through a consult request regarding a specific aspect of a product (e.g., indication, formulation, design, performance).

The following are examples of scenarios in which staff from more than one FDA center may need to access and review an MF to support review of the referencing submission(s):

- A CDER-led drug-device combination product (e.g., drug-filled autoinjector) regulatory submission references a CDER MF that contains information about the container closure system/device ***constituent part***. CDER will need to access the MF to complete their review of the referencing submission as it relates to the container closure system/device constituent part. CDRH will need to access the MF to complete a consult request from CDER about the device constituent part.

- A CDRH-led drug-device combination product (e.g., drug-eluting stent) regulatory submission references a CDER MF that contains information about the drug constituent part. CDRH will need to access the MF to complete their review of the referencing submission as it relates to the drug constituent part. CDER will need to access the MF to complete a consult request from CDRH about the drug constituent part.

- An MF contains information regarding the container closure system of a product. CDER receives drug regulatory submissions that reference the MF. CBER receives biological product regulatory submissions that reference the MF. CVM receives animal drug regulatory submissions that reference the MF. All three centers will need to access the MF for their respective products to complete their reviews of the referencing submissions.

- An MF contains information about a component (e.g., drug substance (active pharmaceutical ingredient), excipient) that will be used in both human and animal drugs.

[8] Not all MFs can be referenced by all submission types. For example, as described in 21 CFR 601.2(g), a biological product in a biologics license application (BLA) under the PHS Act may not rely on an MF for information regarding a drug substance, drug substance intermediate, or drug product. See the Final Rule: Biologics License Applications and Master Files (89 FR 9743, February 12, 2024) at https://www.federalregister.gov/documents/2024/02/12/2024-02741/biologics-license-applications-and-master-files.

CDER receives drug regulatory submissions that reference the MF. CVM receives animal drug regulatory submissions that reference the MF. Both centers will need to access the MF for their respective products to complete their reviews of the referencing submissions.

- An MF describes facilities or manufacturing processes used during the development of drugs. CBER receives drug regulatory submissions (e.g., new drug applications (NDAs)) that reference the MF. CDER receives drug regulatory submissions (e.g., NDAs) that reference the MF. Both centers will need to access the MF for their respective products to complete their reviews of the referencing submissions.

Applicants and sponsors can cross-reference an MF that resides in any medical product center, making it possible to reference the information it contains without the applicants and sponsors having access to its contents. Historically, this has raised questions about which center should receive an MF to be referenced by submissions across multiple centers. For example, when MFs contain information about the device constituent part of a CDER-led combination product, some MF holders have submitted the MF to CDER and others to CDRH. Although the MF can be referenced by a CDER-led combination product submission regardless of its hosting center, establishing a consistent process for designating which center should receive these MFs is expected to enhance efficiency for both MF holders and FDA reviewers.

III. DETERMINING THE HOSTING CENTER FOR A MASTER FILE

When determining the recommended hosting center for an MF, holders should consider the following:

- The purpose of the MF information (e.g., to provide proprietary design or testing information that only addresses the device constituent part of a combination product or to provide proprietary information that addresses a specific information request for a referencing submission);

- Which center will receive the referencing submission; and

- Whether the MF will support a combination product submission.

Based on this information, the two subsections that follow outline FDA's recommendations for determining the hosting center of the MF (see Appendix for examples of FDA's recommendations).[9] There may be scenarios in which the MF holder does not have sufficient information to determine to which center an MF should be submitted. MF holders can engage FDA if they cannot determine the appropriate hosting center for an MF.

[9] Exceptions may occur and are handled on a case-by-case basis.

A. Recommendations for Where to Submit Master Files Supporting Regulatory Submissions for Combination Products

When an MF contains information that will support a regulatory submission for a combination product, the recommended hosting center is generally determined based on the lead center and which constituent part is the subject of the MF. MFs that will be referenced by regulatory submissions for combination products should typically include information about only one constituent part of the combination product.

- If an MF contains information about the constituent part of a CBER-led combination product, CBER is the recommended hosting center, regardless of whether the information is related to a biological product, drug, or device constituent part.

- If an MF contains information about the constituent part of a CDER-led combination product, CDER is the recommended hosting center, regardless of whether the information is related to a drug, biological product, or device constituent part.

- If an MF will be used to support a CDRH-led combination product and the MF contains information regarding the device constituent part, CDRH is the recommended hosting center. If the MF contains information regarding the biological product constituent part or drug constituent part, CBER or CDER is the recommended hosting center depending on where the constituent part would be regulated if it were a standalone product (e.g., if the constituent part would be regulated by CBER, then CBER is the recommended MF hosting center).[10]

Table 1 summarizes FDA's recommendations for determining the hosting center when an MF will be referenced by a combination product regulatory submission.

Table 1

Lead center for the referencing submission	Combination product constituent part described in the master file	Recommended hosting center
CBER	Any constituent part	CBER
CDER	Any constituent part	CDER
CDRH	Biological product constituent part or drug constituent part	CBER or CDER*
CDRH	Device constituent part	CDRH

*CBER and CDER both regulate biological products and drugs; therefore, the hosting center is dependent on the center where the constituent part would typically be regulated.

[10] On June 30, 2003, FDA transferred some of the therapeutic biological products that had been reviewed and regulated by CBER to CDER. CDER now has regulatory responsibility, including premarket review and continuing oversight, over the transferred products. See a list of identified categories of biological products at https://www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research.

In rare cases, the constituent parts of a combination product may be marketed under two applications in two different centers. In this scenario, when an MF contains information that will support one of the constituent parts, the recommended hosting center of the MF is the center that will be receiving the referencing submission for that constituent part. For example, if a combination product is composed of a drug constituent part being marketed under an NDA and a device constituent part being marketed under a premarket approval application (PMA), an MF referenced by the NDA should be submitted to the center receiving the NDA and an MF referenced by the PMA should be submitted to the center receiving the PMA.

B. Recommendations for Where to Submit Master Files Supporting Regulatory Submissions for Non-Combination Products

When an MF contains information that will support a referencing submission that is not for a combination product, the recommended hosting center of the MF is the center that will be receiving the referencing submission.

There are instances in which an MF could be referenced by non-combination product regulatory submissions in more than one center (e.g., if an MF contains information about an inactive ingredient that will be used in both CBER-regulated biological products and CDER-regulated drugs). In this scenario, the center that will receive the first referencing submission is the recommended hosting center for the MF. Coordination between MF holders and applicants/sponsors of referencing submissions can facilitate prompt determination of the center receiving the first referencing submission. The exception to this is when an MF will be used to support both CVM-regulated animal drugs and CDER- or CBER-regulated human drugs or biological products. In this instance, the human medical product center (i.e., CDER or CBER) is the recommended hosting center for the MF. Additionally, FDA discourages the submission of an MF to a human medical product center if the MF will only support animal drugs reviewed by CVM.

GLOSSARY

The following terms are defined for the purposes of this guidance document:

Authorized party: A person or entity (user) who is permitted to incorporate by reference all or any specific part(s) of a master file (MF) to support regulatory submissions to FDA. The authorized party may be a sponsor, applicant, or another MF holder.

Combination Product: A product comprised of two or more different types of products (i.e., a combination of a drug, device, and/or biological product with one another) (see 21 CFR 3.2(e)).

Constituent Part: A drug, device, or biological product that is part of a combination product (21 CFR 4.2).

Cross-Center Master File: An MF that would be accessed by more than one center.

Hosting Center: The FDA center where the MF is located.

Lead Center: The center that has primary review responsibility for the regulatory submission.

Letter of Authorization (LOA): A letter from the MF holder or designated agent or representative that authorizes an applicant, sponsor, or another MF holder to incorporate by reference all or part of the MF's contents to support a regulatory submission or another MF. The LOA also authorizes FDA to review applicable portions of the MF in support of an authorized party's submission or MF. An LOA does not give an authorized party permission to view or access an MF.

Master file (MF): A voluntary submission to FDA used to provide confidential, detailed information including, for example, information about facilities, processes, or articles used in the manufacturing, processing, packaging, and/or storing of one or more regulated articles.[11] MFs can contain other types of information as well (e.g., nonclinical evaluations such as toxicology information, shared system REMS (risk evaluation and mitigation strategy)).

- Master files hosted in the Center for Biologics Evaluation and Research (CBER) are referred to as Master Files (MFs). They can be Type II, III, IV, or V Drug Master Files (DMFs)[12] or Master Files for Devices (MAFs).
- Master files hosted in the Center for Drug Evaluation and Research (CDER) are referred to as DMFs. They can be Type II, III, IV, or V.[13]
- Master files hosted in the Center for Devices and Radiological Health (CDRH) are referred to as Master Files for Devices (MAFs).
- Master files hosted in the Center for Veterinary Medicine (CVM) are referred to as Veterinary Master Files (VMFs) or Public Master Files (PMF). VMFs can be Type II, III,

[11] See footnote 5 for links to center-specific MF information.

[12] For information on the types of master files, see the draft guidance for industry *Drug Master Files* (October 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[13] Ibid.

IV, V, VI, VII, or VIII.[14] PMFs are CVM MFs that are available to the public. For example, PMFs may contain safety and effectiveness information generated by researchers in other government agencies or academia that has been made possible with public funds.

Master File Holder: The organization or person submitting the MF. The MF holder might authorize one or more parties to reference the information contained in an MF.

Medical Countermeasure Master File (MCM MF): A master file that contains data or information that is integral to the MCM indication when referenced, reviewed, and relied upon for the approval, licensure, classification, clearance, conditional approval, or authorization of the MCM submission, as defined in section 565B(f)(2) of the FD&C Act.

Referencing Submission: Any regulatory submission or another MF that was submitted to the Agency and is referencing information contained in an MF.

Regulatory Submission: Includes, but is not limited to, initial, supplements to, and amendments to: investigational new drug applications (IND), new drug applications (NDA), abbreviated new drug applications (ANDA), submissions to (generic) investigational new animal drug ((J)INAD) files, (abbreviated) new animal drug applications ((A)NADA), investigational device exemption (IDE) applications, premarket approval applications (PMA), de novo requests, premarket notifications (510(k)), and biologics license applications (BLA).

[14] For information on the types of MFs, see https://www.fda.gov/animal-veterinary/development-approval-process/veterinary-master-files.

APPENDIX: EXAMPLES OF HOSTING CENTER RECOMMENDATIONS

The hypothetical examples in this section illustrate considerations regarding where MF holders should submit MFs. This section is not intended to reflect a complete analysis of all possible scenarios.

- A drug-filled autoinjector (a CDER-led drug-device combination product) regulatory submission will reference an MF that contains information about the container closure system/device constituent part. Submit the MF to CDER.

- A drug-eluting stent (a CDRH-led drug-device combination product) regulatory submission will reference an MF that contains information about the drug coating (a drug constituent part). As a standalone drug, the drug would have been reviewed by CDER. Submit the MF to CDER.

- An MF contains information about the container closure system of a product. CDER will be receiving a drug regulatory submission that will reference the MF. CBER will be receiving a biological product regulatory submission that will reference the MF. CVM will be receiving an animal drug regulatory submission that will reference the MF. Submit the MF to either CDER or CBER depending on which center will be receiving the first referencing submission.

- An MF contains information about a drug substance (active pharmaceutical ingredient) that will be used in both human and animal drugs. CDER will be receiving a drug regulatory submission that will reference the MF. CVM will be receiving an animal drug regulatory submission that will reference the MF. Submit the MF to CDER.

- An MF describes the facilities or manufacturing processes used during the development of drugs. CBER will be receiving drug regulatory submissions (e.g., NDAs) that will reference the MF. CDER will be receiving drug regulatory submissions (e.g., NDAs) that will reference the MF. Submit the MF to either CDER or CBER depending on which center will be receiving the first referencing submission.

- A combination product will be composed of a laser system (a device constituent part) marketed under a PMA that is intended to be used with a specific light activated drug (a drug constituent part) marketed under an NDA. The PMA being submitted to CDRH will reference an MF that contains information about the packaging materials for the laser system. Submit the MF to CDRH.

- An MF contains information regarding a syringe. The syringe will receive marketing authorization as a standalone device through a 510(k) to CDRH. The syringe will also be co-packaged with a drug and receive marketing authorization through an NDA to CDER. Both the 510(k) and NDA will reference the MF. Submit the MF to the center that will be receiving the first referencing submission.