SOPP 8301: Receipt and Processing of Master Files

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide to the Center for Biologics Evaluation and Research (CBER) staff for the administrative processing and review of Master Files (21 CFR 601.51(a)), Device Master Files[1] (21 CFR 814.20(c)), and Drug Master Files (21 CFR 314.420). This SOPP will generally use the inclusive term “master file” (MF), making distinctions between the different types when necessary.

II. Scope

This SOPP applies to original MF submissions submitted to CBER and their respective technical and administrative amendments, including annual reports (ARs) and letters of authorization (LOAs).

III. Background

A. Master Files are used to provide confidential, detailed information about facilities, processes, components, raw materials, etc., which may be used in the

[1] Note the Center for Devices and Radiological Health (CDRH) refers to device master files as MAF. This SOPP will use the term “device MF”.

manufacture, processing, packaging, and storage of one or more biologic, drug, and device products. A MF allows a manufacturer to protect its intellectual information from disclosure to its development or manufacturing partner while complying with regulatory requirements for disclosure of manufacturing process information to the Agency. The information submitted in a MF may be used to support regulatory submissions including an investigational application [Investigational New Drug Application (IND), Investigational Device Exemption (IDE)], formal meetings [Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT), Type A, B, C], another MF, Q-submissions, and marketing applications and notifications [Biologics License Applications (BLA)[2], Biosimilar Biological Product Application [351(k) BLA], New Drug Applications (NDA), Abbreviated New Drug Applications (ANDA)[3], Premarket Approval (PMA), Premarket Notification [510(k), De Novo Request], and Humanitarian Device Exemption (HDE)]. However, MFs may **not** be used to provide information specifically required to be supplied in marketing applications, supplements, and notifications (e.g., product correspondences).[4]

B. CBER categorizes four[5,6] types of MFs:

1. Type II[3]: information on the drug substance, drug substance intermediate, drug product, and material used in their preparation, or drug product[4];

2. Type III: packaging material;

3. Type IV: information on excipient, colorant, flavor, essence, or material used in their preparation; and

4. Type V: FDA-accepted reference information that is not covered by Types II through IV. For example:

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[2] A BLA holder is expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license. For biological products in BLAs under the PHS Act, applicants may not incorporate information about drug substance, drug substance intermediate, or drug product by reference to a master file; rather, such information must be submitted directly to the BLA.

[3] For additional processes, policies, and guidance that are specific to Type II active pharmaceutical ingredient (API) Drug MFs intended to support ANDA reviews, refer to *Completeness Assessments for Type II API DMFs Under GDUFA Guidance for Industry* and *JA 925.01 ANDA Applications - Initial Processing through Final Action*.

[4] For biological products in BLAs under the PHS Act, applicants may not incorporate information about drug substance, drug substance intermediate, or drug product by reference to a master file; rather, such information must be submitted directly to the BLA. However, INDs may incorporate information about drug substance, drug substance intermediate, or drug product by reference to a master file.

[5] Type I Drug MFs (relate to the manufacturing site, facilities, operating procedures, and personnel) are no longer accepted per a Final Rule published January 12, 2000 (65 FR 1776). This information may be included in a Type V MF.

[6] Master files are described or mentioned in different regulations in the context of drugs (21 CFR 314.420), biologics (21 CFR 601.51(a)), and devices (21 CFR 814.20(c)). However, CBER categorizes MFs according to the types defined for drug master files in 21 CFR 314.420, regardless of whether the MF contains information on or is intended to support a drug, biologic, or device submission/application.

- Non-clinical study data
- Clinical study data (e.g., clinical data collected outside the United States)
- Contract packaging, manufacturing, testing, sterilization, etc. (including information regarding other medical products that are manufactured/processed in the facility)
- All device master files are categorized as Type V MFs. Device master files may contain detailed information regarding specific manufacturing facilities, processes, methodologies, or components used in the manufacture, processing, or packaging of a medical device. They may also provide information regarding finished medical devices.

IV. Definitions

A. MF Holder - A person/entity that owns a MF

B. Agent/Authorized Representative - A legal entity, whether a company or an individual, that is not employed by the MF holder but is appointed to act on behalf of a MF holder

C. MF Status:

1. **Active -** MF is available for reference by another regulatory submission.

2. **Closed -** MF is no longer available for reference by another regulatory submission.

D. Sponsor - A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.

E. Applicant - Any person who submits a marketing application to FDA.

F. Authorized party - Any person or entity who is authorized to reference a MF. May be a sponsor, applicant, or another MF holder.

G. Letter of Authorization (LOA) - A signed and dated letter from the MF Holder, or designated agent or authorized representative, to the authorized party, permitting FDA to review the information in the MF in support of another regulatory submission.

H. Subsequent submission - Additional information and reports submitted to a MF (e.g., Technical Amendments, Administrative Amendments, LOAs, Annual Reports).

I. Pre-IND - A formal interaction with FDA regarding potential or planned Investigational New Drug.

J. Q-submission - A formal interaction with FDA regarding a potential or planned device submission or device constituent.

V. Policy

A. General:

1. A MF is neither approved nor disapproved**.**

2. A MF is not a substitute for an investigational application [IND, IDE] or a marketing application/notification [BLA, 351(k) BLA, ANDA, NDA, 510(k), De Novo, PMA, or HDE] or amendment/supplement to any of these. It is not a stand-alone document and is ordinarily not independently reviewed by the FDA. Technical contents of a MF are reviewed only in the context of a referencing regulatory submission.

3. MFs may also be reviewed in preparation for inspections associated with a referencing regulatory submission; as such, facilities associated with the MF may also be subject to inspection.

4. CBER-generated regulatory communications are only sent to recipients via secure email. Therefore, MF submitters should follow *SOPP 8119: Use of Email for Regulatory Communications* to request a secure email account.

5. A MF generally should not combine different types of information that would otherwise be categorized under two different MF types (e.g., a single MF should not contain both drug substance chemistry, manufacturing, and controls (CMC) information and clinical data that would otherwise be submitted as Type II and Type V master files).

Note: Master file holders who are unsure of which Type of MF their content aligns with, or if they have content that could align with more than one MF Type, should discuss their concerns with the appropriate CBER product office prior to their submission.

B. MF Submission

1. Each MF submission should contain a cover letter, administrative information about the submission, and the respective technical information, as defined in *FDA's Draft Guidance for Industry: Drug Master Files*. If the MF is submitted by an agent/authorized representative, a cover letter from the agent/ authorized representative can replace the MF Holder's cover letter. A completed FDA Form 3938 should also be submitted with each MF submission (original and subsequent submissions). A link to the instructions for completing FDA Form 3938 can be found in the References section below.

    a. Although FDA Form 3938 is titled "Drug Master File", device MF holders should also use the form when submitting device MFs to CBER.

2. Most original MFs and subsequent submissions that are no larger than 10 GB must be submitted electronically through the Electronic Submissions Gateway (ESG) using the electronic Common Technical Document (eCTD) format. There are some exceptions to this procedure (e.g., submissions of Type III MFs); see the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

    a. MFs and subsequent submissions to MFs that are larger than 10 GB, as well as any submission that is not required to be submitted in eCTD format, can be submitted using the ESG (see the *Guidance for Industry: Providing Regulatory Submissions in Alternate Electronic Format Guidance for Industry*) or should be mailed on electronic media to the following address:

        FDA/CBER
        Document Control Center
        10903 New Hampshire Avenue
        Building 71, Room G112
        Silver Spring, MD 20993-0002

    b. Device MFs and subsequent submissions should be submitted to CBER's Document Control Center at the mailing address noted above. FDA recommends submitting these documents per the electronic copy (eCopy) *Guidance for Industry and Food and Drug Administration Staff: eCopy Program for Medical Device Submissions*. An eCopy is an electronic version of a medical device submission stored on a compact disc (CD), digital video disc (DVD), or a flash drive. In lieu of an eCopy, device MFs subsequent submissions may also be submitted as paper copies to the mailing address above. Device MF holders may also consider submitting the device MF through the ESG in eCTD format.

C. Master File Assignment to a CBER Office

1. The CBER office that the MF is assigned to is determined on a case-by-case basis and will depend in part on the subject of the MF and the jurisdiction of any of the regulatory submission(s) authorized to reference the MF at the time of original MF receipt. A MF may be transferred to a different CBER Office as needed based on jurisdiction of future regulatory submission(s) authorized to reference the MF.

2. Although a MF may be assigned to one CBER office, the MF can be referenced by regulatory submissions submitted to other CBER offices as well as other centers within FDA.

D. Master File Review

1. Administrative review of an original MF is intended to determine whether the necessary administrative elements are present. If the administrative information is complete and acceptable, FDA will send an acknowledgement letter to the MF holder (and agent, if applicable) listing the MF number, subject (title), type, and holder's name as specified in the cover letter. If the administrative information is incomplete, FDA will contact the MF holder (and the agent, if applicable) to request the missing information. FDA does not send acknowledgement letters for subsequent submissions (e.g., amendments, reports, additional LOAs).

2. Before FDA can review MF information in support of a referencing regulatory submission:

a. The MF Holder:

i. Must submit a copy of an LOA to the MF. If the referencing submission's sponsor/applicant is also the MF Holder, the MF Holder should still supply an LOA. The LOA should identify the MF number, the authorized party, and referencing submission (e.g., submission number or title). The LOA may also contain a description of what information the referencing submission is authorized to reference, and the location of that information in the MF (e.g., volume, section, amendment number, page, etc.).

ii. Must provide a copy of the LOA to the authorized party, for inclusion in the referencing submission.

b. The authorized party:

i. Must submit a copy of the LOA in the referencing regulatory submission.

ii. Should communicate with the MF holder to ensure the MF is current.

3. A regulatory submission should not cross reference a MF by cross referencing another regulatory submission that cross references that MF. The sponsor/applicant should obtain their own LOA to authorize reference of the MF to support their regulatory submission[7].

4. An LOA does not give an authorized party permission to view or access the MF. Hence, during review of a MF in support of a referencing submission, separate internal review memos are typically prepared for the MF and the referencing submission to ensure that proprietary information contained in the MF is not inadvertently disclosed to unauthorized parties in response to a Freedom of Information Act (FOIA) request.

5. A regulatory submission should be complete at the time of receipt, including cross reference(s) to a MF(s) and an accompanying LOA(s).[8] In general, the sponsor/applicant of regulatory submissions should not amend their submission during the course of review to incorporate new information by reference to a MF, as there will likely not be sufficient time to review the cross-referenced information.

6. When necessary, CBER may request consult reviews of MF technical/quality information in the context of a referencing submission from subject matter experts in other FDA centers (e.g., CDRH, CDER, CVM, etc.), per the established procedures (refer to *SOPP 8001.5: Inter-Center Consultative Review Process*).

7. If during review, the MF is deemed to be deficient to support a specific referencing regulatory submission, a 'Master File Deficiency Letter [per

[7] Notably, some Type II MFs can have eCTD requirements waived if they are cross referenced only by non-commercial INDs. The Type II MF is no longer eligible for the eCTD waiver if they issue an LOA(s) to support a commercial IND. It is inappropriate for a commercial IND to cross reference a non-commercial IND that cross-references a waived Type II MF to circumvent eCTD requirements for the MF. For more information on eCTD requirement waivers, refer to the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications*, as well as *JA 830.01: Procedures for Requests for Waivers from eCTD Submission Requirements*.

[8] For example, per 21 CFR 314.50, 21 CFR 601.2, *SOPP 8401: Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA)*, and *SOPP 8404: Refusal to File Procedures*, an original application submission is expected to be complete. An application that cross references a MF but lacks an accompanying LOA may be considered incomplete and may affect the filing decision.

application review]' will be sent to the MF holder. At the same time, FDA will notify the authorized party that the MF is insufficient to support their submission. The general subject of the deficiency is identified, but details of the deficiency are disclosed only to the MF Holder.

8. If the information in the MF is adequate to support the referencing regulatory submission, but FDA has recommendations for the MF holder regarding additional information to include in the MF, an Advice/Information Request letter is sent to the MF holder only.

9. In accordance with the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 (PAHPAIA), if a medical countermeasure (MCM) master file was directly cross referenced by an MCM submission and reviewed and relied upon in support of an approval/ licensure/ authorization/ classification/ clearance/ conditional approval of a medical countermeasure product or a new indication to an approved medical countermeasure product, an MCM MF Notification letter is sent to the MF holder.

E. MF Amendments

1. Any administrative or technical information changes should be submitted as MF amendments.

2. A completed FDA Form 3938 should also be submitted with each amendment.

3. MF holders must notify affected authorized parties in advance of any MF changes to technical information in the MF and provide sufficient information to enable authorized parties to determine the appropriate reporting procedure for their regulatory submissions. The MF holder should provide this notification before making changes to the technical information in the MF.

   a. The cover letter of a MF amendment for changes to technical information should provide a statement identifying the affected authorized parties and confirming that they were notified of the change.

F. Annual Reports (ARs)

1. The MF Holder should provide an AR on the anniversary date of the original submission.

2. A completed FDA Form 3938 should be submitted with the AR.

3. Annual reports should contain appropriate administrative information, a tabulated summary of all administrative and technical changes made to the MF in the reporting period (including amendment number and date), a current list of authorized parties (as noted above), and a list of parties whose authorization has been withdrawn and the dates of withdrawal.

4. ARs should **not** be used to report new (previously unreported) changes to technical information in the MF. If it is necessary to submit changes to the MF and an AR at the same time, they must be submitted to the MF separately (i.e., separate submissions for the amendment and AR).

5. ARs should include a cover letter and a statement of commitment signed by the MF holder stating that the information in the MF is current and that the holder will comply with statements made in the MF. The following statement of commitment is recommended for inclusion in this letter:

   [MF Holder] confirms that [MF Number] is current and [MF Holder] will comply with statements made within it. [MF Holder] will notify FDA through an amendment to [MF Number] of any addition, change, or deletion of information in the MF. [MF Holder] will also notify [Authorized Party] in writing that an addition, change, or deletion of information has been made to the MF.

6. Failure to submit ARs can cause delays in FDA review of a pending, referencing regulatory submission and may result in regulatory action on any active cross-referencing regulatory submissions or closure of a MF.

G. Closure of a MF

1. There are two mechanisms for closure of a MF:

   a. The MF Holder may request that the MF be closed (i.e., inactivated or withdrawn) by submission of a Closure Request in an amendment.

      - When the MF holder intends to close a MF, the MF holder should inform all authorized parties currently referencing the MF of the intent to close the MF prior to submitting the closure request to FDA. The MF holder should confirm that they informed all authorized parties in the cover letter of the Closure Request.

   b. A MF may be closed by FDA if the MF cannot be confirmed as current and the MF holder has not responded to FDA requests to update the MF (e.g.,

submit an overdue AR). FDA will notify the holder or agent, as applicable, of this action.

- If the MF holder receives a notification from FDA that the MF has been closed due to inactivity and non-response to a request from FDA to update the MF, the MF holder should inform all authorized parties currently referencing that the MF is closed and can no longer be referenced. The MF holder should respond to the FDA closure notification to confirm that that they informed all authorized parties.

2. A Closed MF status can be returned to Active status only by submission of a request for reactivation (to the same MF Submission Tracking (STN)), containing a complete, updated resubmission of the MF.

VI. Responsibilities

A. Document Control Center (DCC):

1. Initiate processing and routing of MF-related submissions upon CBER receipt.

B. Office of Regulatory Operations (ORO), Division of Informatics and Information Technology (DIIT), Regulatory Information Branch (RIB):

1. Process requests from sponsor/applicant for pre-assigned tracking numbers. Provide number to the sponsor/applicant within two business days of the request.

2. Characterize original MFs and subsequent submissions in the appropriate CBER system.

3. Run reports to assess if any MFs have outstanding annual reports. Coordinate (with RPMs) the issuance of Report Requests to the MF Holders.

C. Regulatory Project Manager (RPM):

1. Conduct administrative review and actions for MFs.

2. Route MF original submissions and amendments to reviewer(s).

3. Ensure routine and timely communications.

4. Facilitate communication with the MF Holder when deficiencies are identified in the MF.

D. Reviewers:

1. Conduct or coordinate technical reviews of MFs as it relates to a referencing regulatory submission review. Technical review team members may include personnel from a Product Office, other CBER offices, and other centers in the agency.

E. Product Jurisdiction Officer (PJO):

1. Assist review staff in locating and obtaining access to MFs that reside in other centers.

2. Assist in identification of appropriate CBER product office that should receive an original MF.

3. Provide support for the inter-center consult request (ICCR) process through:

   a. Identification of the appropriate reviewer office or division for MFs when a consult is needed

   b. Assistance with the preparation of and follow up for requested consults

VII. Procedures

A. Original Submissions

1. Receipt and Acceptance:

   a. When applicable, pre-assign a submission tracking number (STN) and identify/notify the appropriate CBER product review office, in accordance with *SOPP 8117: Issuing Tracking Numbers in Advance of Electronic Submissions in eCTD Format*. Consult CBER product review offices and/or PJO if it's unclear which CBER product review office should receive the MF. **[RIB]**

   b. Receive and upload all original MFs either through ESG or via mail on electronic media (ESG or eCopy/paper via mail) and assign an STN (if an STN was not pre-assigned). **[DCC]**

   c. Characterize the MF in the appropriate regulatory system. **[RIB]**

2. Submission Routing and Assignment

a. Route the MF to the appropriate CBER product office. Consult CBER product review offices and/or PJO if it's unclear which CBER product review office should receive the MF. **[DCC/automated system]**

b. Assign an RPM to the MF. **[RPM Leadership]**

3. Review Administrative Elements

a. Review administrative elements, including FDA Form 3938 and any LOA(s) included with the submission, to ensure that the subject, holder name, and MF type match the information listed for that MF number in the CBER system. Confirm the presence of administrative elements such as the holder's address, agent's address (if applicable), and appropriate submission type. Contact the MF holder/agent for any missing administrative information. **[RPM]**

- If the MF holder does not have secure email, contact them by phone to notify them of the missing administrative information and our inability to communicate with them via email. The submitter should follow *SOPP 8119: Use of Email for Regulatory Communications* to request a secure email account. **[RPM]**

b. Issue an acknowledgement letter via secure email/fax within 30 days of assignment and upload to the appropriate regulatory system. **[RPM]**

4. Review MF in Support of a Cross Referencing Submission

a. Assign a reviewer to the MF upon receipt of a submission that references a MF and includes an LOA. The reviewer assigned to the MF may be a reviewer from the review team assigned to the referencing submission. **[Branch Chief or Designee]**

b. Initiate review of the MF in the context of that referencing submission. **[Reviewer]**

i. If the referenced MF is not up to date (e.g., no recent ARs, etc.), request that the MF holder update their MF to ensure the content is current and that the holder will comply with the statements made in the MF.

ii. When necessary, request consult reviews of MF technical information in the context of the referencing regulatory submission from subject

matter experts in CBER and/or other FDA centers (e.g., CDRH, CDER, CVM, etc.), per the established procedures (see *SOPP 8001.5: Inter-Center Consultative Review Process*). **[Reviewer, RPM]**

iii. For assistance in locating and obtaining access to MFs that reside in other centers, contact the PJO at CBERProductJurisdiction@fda.hhs.gov. **[Reviewer, RPM]**

B. Subsequent Submissions (Technical Amendments, Administrative Amendments, LOAs, Annual Reports)

1. Receive subsequent submissions to MFs through ESG or via mail on electronic media. Assign a second level STN. Route the subsequent submission to the appropriate CBER product review office. **[DCC]**

2. Characterize the subsequent submission as an amendment to the associated original MF. **[RIB]**

3. Review administrative elements of subsequent submissions, including FDA Form 3938 and LOA(s), to ensure that the subject, holder name, and MF type match the information for the information listed for that MF number in the CBER system. Confirm the presence of administrative elements such as the holder's address, agent's address (if applicable), and appropriate submission type, and if applicable, amendment type (e.g., change of holder, change of MF subject). Contact the MF holder (and agent, if applicable) if administrative issues are noted. **[RPM]**

4. If a sponsor/applicant that references a MF submits an amendment to their regulatory submission indicating that the MF holder notified them of an amendment(s) to the MF contents that affects their referencing submission, the reviewer(s) assigned to the referencing submission initiates a review of the MF amendment(s) in the context of that referencing submission. **[Reviewer]**

a. If a sponsor/applicant of a regulatory submission includes a new reference (and LOA) to a MF that has pre-existing amendments, the reviewer(s) assigned to the referencing submission initiates a review of the MF and its amendments in the context of that referencing submission.

b. When necessary, request consult reviews of MF technical/quality information in the context of a referencing submission from subject matter experts in CBER and/or other FDA centers (e.g., CDRH, CDER, CVM,

etc.), per the established procedures (refer to *SOPP 8001.5 Inter-Center Consultative Review Process*).

5. For Annual Reports, review and confirm that it contains the FDA Form 3938, a cover letter with a statement of commitment, and a tabulated summary of all administrative and technical/quality changes made to the MF for the reporting period (including amendment number and date). **[RPM/Reviewer]**

C. Memos and documentation

1. Prepare separate internal review memos for the MF and the referencing submission as needed. **[Reviewer(s)]**

a. The only reference to the MF in the reviewer's memo for the referencing submission should be a statement that identifies the MF being referenced, the purpose of referencing the MF, whether the information provided in the MF is adequate to fulfill this purpose, whether a letter will be issued to the MF holder at the completion of the review, and a reference to the MF review memo for more details on the review.

- The only reference to the referencing submission in the separate MF review memo should be the submission number. Though this memo may vary in format it must include any information about the submission required to provide the necessary context for the review of the MF [e.g., product description, indication for use, phase of study (e.g., Phase 1/2/3, Early Feasibility, Feasibility, Pivotal), type of submission, purpose of referencing the information in the MF (including specific questions if the referencing submission is a formal meeting with FDA)].

2. After the reviews of the MF and referencing regulatory submission are complete, send the RPM any comments to communicate to the MF holder and referencing submission sponsor/applicant, clearly distinguishing which comments are for the MF holder and which comments are for the referencing submission sponsor/applicant. **[Reviewer]**

D. Letters:

1. If during review, the MF is deemed to be deficient to support a specific referencing submission:

a. Send a Master File Deficiency Letter to the MF holder. **[RPM]**

b. Simultaneously notify the authorized party of the referencing submission that the referenced MF is not adequate to support their submission. **[RPM]**

i. For investigational applications, notify the sponsor initially via email/telephone and subsequently issue a deficiency letter per applicable timelines (e.g., clinical hold, partial clinical hold, disapproval, conditional approval, etc.)

ii. For formal meetings and Q-submissions, notify the meeting requester in the preliminary written responses.

iii. For marketing applications, issue a deficiency letter (e.g., Complete Response, Major Deficiency, etc.).

c. Ensure communications and letter(s) are uploaded through CBER Connect. **[RPM]**

2. If the information in the MF is adequate to support the referencing submission, but FDA has recommendations for the MF holder regarding additional information to include in the MF, send an Advice/Information Request letter to the MF holder only. Ensure letter is uploaded through CBER Connect. **[RPM]**

3. If an MCM MF was directly cross referenced by a MCM submission and reviewed and reviewed and relied upon in support of an approval/ licensure/ authorization/ classification/ clearance/ conditional approval of an MCM submission, send an MCM MF Notification letter to the MF holder. **[RPM]**

4. If the MF holder has not submitted an AR within the last year, issue an Annual Report Request letter and upload through CBER Connect. **[RPM/RIB]**

E. Closing a MF

1. MF Holder Request for Closure

a. Upon receipt of a MF holder's request for closure, characterize the amendment as a closure request in BIRAMS. **[RIB]**

i. Determine whether there are any submissions/ applications currently referencing the MF. **[RPM]**

ii. If there are no submissions/ applications currently referencing the MF issue a 'MF Closure' letter to the MF Holder, acknowledging their

request to close the MF. Upload the letter to the appropriate regulatory system. Ensure the correct communication code is entered into the regulatory system to reflect the correct MF status. **[RPM]**

iii. If there are submissions/applications currently referencing the MF, confirm that the MF holder informed authorized parties of the intent to close the MF prior to issuing the MF Closure letter, acknowledging their request to close the MF. **[RPM]**

2. MF not Current

- If the MF holder fails to annually update the MF to assure FDA that the MF is current and also fails to respond to FDA's requests to update the MF (e.g., submit and overdue AR), consideration should be given to closing the MF (e.g., issuing a 'MF Closure' letter to MF holder, noting that the MF was closed due to inactivity) and/or taking regulatory action on any active cross-referencing regulatory submissions. **[RPM/RIB]**

VIII. Appendix

N/A

IX. References

A. The references below are CBER Internal:

1. SOPP 8001.5: Inter-Center Consultative Review Process

2. JA 925.01: ANDA Applications - Initial Processing through Final Action

3. JA 830.01: Procedures for Requests for Waivers from eCTD Submission Requirements

B. References below can be found on the Internet:

1. Guidance Documents:

a. Draft Guidance for Industry: Drug Master Files

b. Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications

c. Guidance for Industry: Providing Regulatory Submissions in Alternate Electronic Format

d. Guidance for Industry: Use of a Drug Master File for Shared System REMS Submissions

e. Guidance for Industry and Food and Drug Administration Staff: eCopy Program for Medical Device Submissions

f. Guidance for Industry: Completeness Assessments for Type II API DMFs Under GDUFA

2. CBER Standard Operating Policies and Procedures (SOPPs)

a. SOPP 8119: Use of Email for Regulatory Communications

b. SOPP 8117: Issuing Tracking Numbers in Advance of Electronic Submissions in eCTD Format

3. FDA Forms and Instructions

a. FDA Form 3938 - Drug Master File (DMF)

b. Instructions for Filling out FDA Form 3938

4. Other Resources

a. Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019.

Information and updates regarding implementation of FDA-related PAHPAIA provisions, including FDA's implementation of the MCM MF provisions, can be found at the following link: MCM-Related Counterterrorism Legislation.

b. Proposed Rule for the use of Master Files in Biologics License Applications

On June 28, 2019, FDA issued a proposed rule regarding the use of MFs by BLAs and by INDs for products that would be subject to regulation under the Public Health Service Act. Information regarding the proposed rule can be found at the following link:

https://www.federalregister.gov/documents/2019/06/28/2019-13753/biologics-license-applications-and-master-files.

X. History

Written/Revised	Approved By	Approval Date	Version Number	Comment
Christian Lynch	Christopher Joneckis, PhD	May 9, 2022	2	Updated to current policies and procedures
CBER Application Policy Task Force	Michael Beatrice	11/1/1993	1	OD-R-4-93 reissued as SOPP 8301 in August 1997. No change to Guide content.