# SOPP 8301: Receipt and Processing of Master Files

**Version**: 5
**Effective Date:** May 7, 2026

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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] 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 [i.e., 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, D], 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).[2]

**B.** CBER categorizes four[4,5] types of MFs:

**1.** Type II[3]: information on a drug substance, drug substance intermediate, and material used in their preparation, or drug product.[2]

**2.** Type III: information on packaging material.

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

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

**a.** Non-clinical study data.
**b.** Clinical study data (e.g., clinical data collected outside the United States)

[2] A Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act is not permitted to incorporate by reference drug substance, drug substance intermediate, or drug product information contained in a master file (21 CFR 601.2(g)(1)) with certain specific exceptions (21 CFR 601.2(g)(2) and (3)). However, INDs may incorporate information about drug substance, drug substance intermediate, or drug product by reference to a MF

[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] Type I Drug MFs (related 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.

[5] MFs 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 MFs 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.

**c.** Contract packaging, manufacturing, testing, sterilization, etc. (including information regarding other medical products that are manufactured/processed in the facility) for drug or biologic constituents.

**d.** All device MFs are categorized as Type V MFs. Device MFs 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. This 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 the authorized party's regulatory submission.

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

## 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, ANDA, NDA, 510(k), De Novo, PMA, or HDE) or amendment/supplement to any of these.

3. Submission of a MF is not equivalent to "registering" a product with FDA and does not convey any type of regulatory decision or regulatory standing in and of itself. Existence of a MF means a firm has submitted a repository of confidential information to FDA that referencing regulatory submission sponsors/applicants can incorporate into their submissions by cross reference.

4. Technical contents of a MF are reviewed only in the context of a referencing regulatory submission.

5. 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.

6. 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.

7. 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).

8. A person/entity who intends to submit a MF to CBER and is unsure of which Type of MF the content of their planned MF submission aligns with, or plans to include content that could align with more than one MF Type, should discuss their concerns with the appropriate CBER product office prior to their submission, if known. If they are uncertain of the appropriate CBER product office, they should direct their question(s) to industry.biologics@fda.hhs.gov, or the CBER product jurisdiction mailbox at CBERProductJurisdiction@fda.hhs.gov. General MF questions (e.g., from a person/entity who intends to submit a MF or cross reference a MF in a planned regulatory submission to CBER) should also be directed to

industry.biologics@fda.hhs.gov.

9. FDA's *Draft Guidance for Industry: Drug Master Files* states that a person who intends to submit a Type V MF to CDER must first submit a letter of intent. A person who wishes to submit a Type V MF to CBER and would like clarification on whether a Type V MF is appropriate may send a letter of intent to industry.biologics@fda.hhs.gov.

10. Generally, the center that a MF should be submitted to is determined by factors such as the subject of the MF and the types of products that would be referencing it. A person/entity who intends to submit a MF and is unsure if they should submit their MF to CBER should contact CBERProductJurisdiction@fda.hhs.gov. If the MF may be referenced by submissions in multiple centers or for a combination product, refer to the FDA draft guidance *Draft Guidance for Industry Cross-Center Master Files: Where to Submit* for additional recommendations.

## B. Master File 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., submission of Type III MFs); see *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 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.** We encourage submission of device MFs and subsequent submissions through ESG in eCTD format. Alternatively, 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.

**c.** A pre-assigned submission tracking number (STN) is required for MFs that will be submitted to CBER in eCTD format, following S*OPP 8117: Issuing Tracking Numbers in Advance of Electronic Submissions in eCTD Format.*

**d.** Sponsors or applicants requesting a waiver from the electronic submission requirements mandated under section 745(A) of the FD&C Act should submit a waiver request to esubprep@fda.hhs.gov. CBER will review the waiver request and respond stating whether the waiver is granted or denied. See also *Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* and *Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*

## C. Master File Assignment to a CBER Office

**1.** The CBER office that a MF is assigned to is determined on a case-by-case basis and depends, 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. Refer to Managing Cross Center Master Files SOP for policies and procedures to use when a regulatory submission

references a MF located in another center.

## 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 a LOA to the MF. The LOA should identify the MF number, the authorized party, and referencing regulatory submission (e.g., submission number or title). The LOA may also contain a description of what information the referencing regulatory submission is authorized to reference, and the location of that information in the MF (e.g., volume, section, amendment number, page).

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

**iii.** If the authorized party and the MF holder are the same, the MF holder should still submit a copy of a LOA to the MF and provide the LOA to the authorized party, for inclusion in the referencing regulatory submission.

**b.** The authorized party:

**i.** Must submit a copy of the LOA in the referencing regulatory submission, even if the sponsor/applicant and the MF holder are the same.

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

**iii.** Will list references to MFs in the Cross References section of any forms required for the type of regulatory submission (e.g., Form FDA 1571,

Form FDA 356h).

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.[6]

4. A 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 regulatory submission, separate internal review memos are typically prepared for the MF and the referencing regulatory 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).[7] In general, the sponsor/applicant of regulatory submissions should not amend their submission during the review cycle 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 regulatory submission from subject matter experts in other FDA centers (e.g., CDRH, CDER, CVM), per the established procedures (refer to *SOPP 8001.5: Inter-Center Consultative Review Process*).

7. If during a review, the MF is deemed to be deficient to support a specific referencing regulatory submission, a Master File Deficiency letter will be sent to the MF holder. FDA will notify the authorized party that the MF is insufficient to support their submission. The general subject of the deficiency may be 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

[6] Notably, some Type II MFs can request eCTD requirements to be 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*.

[7] 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 is expected to be complete. An application that cross references a MF but lacks an accompanying LOA may be considered incomplete, which may affect the filing decision.

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. Master File Amendments

**1.** Any administrative or technical information changes should be submitted as MF amendments. Recommendations regarding common types of administrative amendments are described in FDA's *Draft Guidance for Industry: Drug Master Files*.

**2.** A completed FDA Form 3938 should 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.

**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 yearly from the 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, and a list of parties whose authorization has been withdrawn as well as 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 technical information amendment and the 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 referencing regulatory submissions or closure of a MF.

## G. Closure of a Master File

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

**a.** The MF holder may request that the MF be closed 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 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 issue a MF Pending Closure letter to notify the holder or agent, as applicable, of intent to close the MF.

- The MF holder may opt to voluntarily submit a Closure Request in response to a “MF Pending Closure” letter from FDA.

- If the MF holder receives a “MF Closure” letter from FDA stating that the MF has been closed (e.g., due to inactivity and non-response to a

request from FDA to update the MF), the MF holder should inform all authorized parties 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 emailing a request for reactivation to RIB at CBERRIB@fda.hhs.gov. After confirmation of receipt of the reactivation request, the MF holder should submit any updated MF information to the MF as an amendment.

## 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 (DI), Regulatory Information Branch (RIB):

1. Process requests from MF holder or agent/authorized representative for pre-assigned tracking numbers. Provide number to the MF holder or agent/authorized representative within two business days of the request.

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

3. Generate reports to assess if any MFs have outstanding annual reports. Coordinate (with RPMs) the issuance of Annual 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. These technical reviews may be provided by subject matter experts from CBER and/or from 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, following *Managing Cross Center Master Files SOP*.

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.

### F. Manufacturers Assistance & Technical Training Branch (MATTB) Staff

1. Receive and respond inquiries from industry about MFs (e.g., questions about the appropriate MF type for the information the plan to submit).

2. Contact CBER subject matter experts as necessary to generate responses to inquiries from industry.

## 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 and assign an STN (if an STN was not pre-assigned). **[DCC, Electronic Submission Processing (ESP)]**

   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, ESP]**

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

**c.** Contact appropriate review group to request assignment of a reviewer to the MF, if necessary. **[RPM]**

**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 STN 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 Regulatory Submission

**a.** Initiate review of the MF technical information in the context of that referencing regulatory submission.
**[Reviewer]**

**i.** If the referenced MF is not up to date (e.g., no recent ARs, the LOA does not state the MF is current), request that the MF holder update their MF to ensure the content is current and that the MF holder will comply with the statements made in the MF. **[Reviewer, RPM]**

**ii.** When necessary, request a consult review(s) 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,), per the established procedures (see *SOPP 8001.5: Inter- Center Consultative Review Process*). **[Reviewer, RPM]**

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

**1.** Receive subsequent submissions to MFs through ESG, via mail on electronic media, or as a paper copy (for device MFs). 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 any LOA(s), to ensure that the subject, holder name, and MF type match the information listed for that MF STN 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/agent for any missing administrative information. **[RPM]**

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

**b.** When necessary, request a consult review(s) of MF technical/quality information in the context of a referencing regulatory submission from necessary subject matter experts in CBER and/or other FDA centers (e.g., CDRH, CDER, CVM,), per the established procedures (refer to *SOPP 8001.5 Inter-Center Consultative Review Process*). **[Reviewer, RPM]**

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. Ensure proprietary information contained in the MF is not inadvertently disclosed to unauthorized parties in response to a FOIA request by preparing separate internal review memos for the MF and the referencing regulatory submission as needed. **[Reviewer]**

    a. The referencing regulatory submission memo should include a statement that identifies the MF being referenced, the purpose of referencing the MF, states whether the information provided in the MF is adequate to fulfill this purpose, states whether a letter will be issued to the MF holder at the completion of the review, and refers the reader to the MF review memo for more details on the review. Concurred referencing regulatory submission review memos should be uploaded to the referencing regulatory submission record only in the appropriate regulatory system.

    b. The MF review memo should identify the referencing regulatory STN and 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., if applicable; 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 regulatory submission is a formal meeting with FDA)]. Concurred MF review memos should be uploaded to only the MF record in the appropriate regulatory system.

2. After the reviews of the MF and referencing regulatory submission are complete, send the RPM any comments (written in Four-Part Harmony; refer to *SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Applications*) to communicate to the MF holder and referencing regulatory submission sponsor/applicant, clearly distinguishing which comments are for the MF holder and which comments are for the referencing regulatory submission sponsor/applicant. **[Reviewer]**

## D. Information Requests:

1. If additional information is needed from the MF holder during review, send an information request with comment(s) (written in Four-Part Harmony) to the MF contact. **[RPM]**

## E. Letters:

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

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

**b.** Simultaneously notify the sponsor/applicant of the referencing regulatory 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).

**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, Additional Information).

**c.** Ensure communications and letter(s) are entered into the appropriate regulatory system and uploaded into the administrative file through CBER Connect. **[RPM]**

**2.** 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, send an Advice/Information Request letter to the MF holder only. Ensure the letter is entered into the appropriate regulatory system and uploaded into the administrative file through CBER Connect. **[RPM]**

**3.** If an MCM MF was directly cross referenced by a MCM submission 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, enter it into the appropriate regulatory system and upload it into the administrative file through CBER Connect. **[RPM/RIB]**

## F. Closing a Master File

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 the appropriate regulatory system. **[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. Enter the letter into the appropriate regulatory system, ensuring the correct communication code is entered to reflect the correct MF status and upload it into the administrative file. **[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. **[RPM]**

2. MF not Current

    a. 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 an overdue AR), consideration should be given to closing the MF (e.g., issuing 'MF Pending Closure" letter and subsequently a 'MF Closure' letter to MF holder) and/or taking regulatory action on any active referencing regulatory submissions. **[RPM/RIB]**

## VIII. Appendix

Not Applicable

## 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

4. FDA's Managing Cross Center MF SOP

**B.** References below can be found on the Internet:

1. FDA Websites

   **a.** Master Files for CBER-Regulated Products

   **b.** Manufacturers Assistance and Technical Training Branch (MATTB)

2. Guidance Documents:

   **a.** Draft Guidance for Industry: Cross-Center Master Files: Where to Submit

   **b.** Draft Guidance for Industry: Drug Master Files

   **c.** Providing Regulatory Submissions for Medical Devices in Electronic Format - Submissions Under Section 745A(b) of the Federal Food, Drug, and Cosmetic Act

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

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

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

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

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

3. 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

**c.** SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Applications

**4.** FDA Forms and Instructions

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

**b.** Instructions for Filling out FDA Form 3938

**5.** 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.** Final Rule: Biologics License Applications and Master Files

On February 12, 2024, FDA issued a final rule (89 FR 9743) amending its regulations to address the use of master files by Biologics License Applications (BLAs). The rule, which became effective March 13, 2024, codifies that BLAs may not reference master files for drug substance, drug substance intermediate, or drug product information, while detailing specific exceptions (21 CFR 601.2(g)).

## X. History

| Written/Revised | Approved By | Approval Date | Version Number | Comment |
|---|---|---|---|---|
| Andrea Gray | Martha Monser RRDL, RABOB/DROP/ ORO | May 7, 2026 | 5 | Minor updates to reflect current regulations, guidance, policies and procedures |
| Andrea Gray | Sonday Kelly, MS, RAC, PMP Director, DROP/ORO | December 14, 2023 | 4 | Editorial corrections and updated to reflect current policies and procedures |

| Written/Revised | Approved By | Approval Date | Version Number | Comment |
|---|---|---|---|---|
| Monser | N/A | February 27, 2023 | 3 | Technical Update for 2023 CBER reorganization |
| 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. |