

SOPP 8404: Refusal to File Procedures

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff to follow for Refuse To File (RTF) determinations for a Biologics License Application (BLA), an Efficacy Supplement or a Prior Approval Manufacturing Supplement (21 CFR 601.2) or a New Drug Application (NDA) or supplemental NDA (21 CFR 314.101(d)(1)-(9)).

II. Scope

- A.** This SOPP applies to BLAs, and associated efficacy or manufacturing supplements, as well as, NDAs, and associated supplemental NDAs for which an RTF decision is made.
- B.** This SOPP does not apply to BLAs subject to the Medical Device User Fee Act (MDUFA) or Abbreviated New Drug Applications subject to the Generic Drug User Fee Act (GDUFA).

III. Background

- A.** RTF is an important regulatory tool to help CBER avoid unnecessary review of incomplete applications and supplements. Incomplete submissions can lead to multiple-cycle reviews and inefficient use of CBER resources and may also delay the review of more complete submissions from other applicants. CBER also believes an RTF action can allow an applicant to begin repair of

critical deficiencies in the submission far sooner than if the deficiencies were identified much later in a complete review action and may lead to more rapid approval of safe and effective products. Applications and supplements accepted for filing should be sufficiently complete to permit a meaningful review.

- B.** Applications and supplements are expected to be complete when received by the Agency. Incomplete applications and some supplements will be subject to an RTF decision.
- C.** Discipline-specific filing checklists are used to ensure a timely and thorough filing review of applications, to provide consistency in applying our RTF authority, and to provide documentation of deficiencies for the RTF letter.
- D.** [Appendix A](#) provides more information regarding how to identify RTF deficiencies compared to deficiencies that are appropriate for inclusion in a Complete Response Action.

IV. Definitions

N/A

V. Policy

- A.** RTF decisions are made on submissions that do not, on their face, contain information required under section 351 of the Public Health Service Act; the Federal Food, Drug, and Cosmetic Act (FD&C Act); or in the FDA regulations (e.g., § 601.2 for BLA and §314.50 for NDA). RTF decisions can therefore be based on findings such as:
 - 1.** Administrative incompleteness, such as clear omission of information or sections of required information;
 - 2.** Scientific incompleteness, such as omission of critical data, information or analyses needed to evaluate safety, purity and potency or provide adequate directions for use; and
 - 3.** Inadequate content, presentation, or organization of information such that substantive and meaningful review is precluded, such as illegibility; failure to translate portions of the application into English; data tabulations (line listings) or graphical displays that are uninterpretable; failure to reference the location of individual data and records in summary reports; absence of protocols for clinical trials; omission of critical statistical analyses or the analysis of a study as planned in the protocol (as opposed to a different, post-hoc analysis).
- B.** CBER's initial decision on whether or not to file an application or supplement will be based upon a threshold determination as to whether the information

submitted to support licensure or approval is sufficiently complete to permit a substantive and meaningful review.

- C. For products submitted under the PDUFA Program, a pre-BLA/NDA meeting occurs whereby the FDA and the applicant agree on the content of a complete application for the proposed indication(s) and identify minor components that may be submitted no later than 30 calendar days after receipt of the original application. Applications are expected to be complete when received by the Agency. Incomplete applications, including applications with minor components not received within the 30 calendar days after receipt of the original application, will be subject to an RTF decision.

VI. Responsibilities

- A. **Branch/Lab Chief, Division Director** – Evaluates the reviewer’s recommendations; concurs/does not concur on recommendation. Writes separate memo for a non-concurrence
- B. **Chair/Regulatory Project Manager (RPM)** – Drafts and finalizes Filing Meeting Summary and Filing or RTF letter; manages RTF process; ensures issuance of the Filing/RTF letter to the applicant
- C. **Office Director, Deputy Office Director** – the Signatory Authority who signs RTF letters
- D. **Review Committee Member** – Reviews submission, recommends fileability of submission, documents recommendation in the filing checklist or memo, discusses the fileability of application with management; reviews draft meeting summary and draft Filing or RTF letter

VII. Procedures

A. Original BLAs, NDAs and Efficacy Supplements

1. Prior to the Filing Meeting

- a. Review the submission as described in *JA 910.06: Completing a Filing Review*. **[Review Committee Members]**
- b. Notify the Chair, RPM, and supervisors (Branch/Lab Chief, Division Director) of the potential of a RTF recommendation. **[Review Committee Members]**
- c. Draft and distribute the Filing Meeting Agenda in preparation for the Filing meeting. **[RPM]**

Note: Ensure the Associate Director for Review Management (ADRM) is invited if there are significant review or potential RTF issues.

- d. Ensure that management is notified immediately upon discovering that a RTF recommendation might be made. **[Chair/RPM]**
- e. Complete the filing checklists, summarize all potential review deficiencies and RTF items in letter ready format in the appropriate section of the checklist. **[Review Committee Members]**
- f. Email the checklists, with the appropriate management copied, to the Chair and RPM prior to the filing meeting. **[Review Committee Members]**
- g. Discuss and decide whether the submission should or should not be filed at the filing meeting. **[Review Committee Members, Branch/Lab Chief, Division Director, Office Director, ADRM]**

Note: If ADRM is unable to attend the filing meeting, discuss the RTF decision with him/her prior to sending the draft RTF letter around for office comment.

Note: if submission will be filed, proceed with review as outlined in *SOPP 8401: Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA)*.

2. After Filing Meeting - Filing Checklists

- a. Update the filing checklist or memo, if needed, and include a rationale if recommending an RTF decision in the appropriate section of the filing checklist or memo. The RTF recommendation must include a list of missing, incomplete, or inaccessible information. **[Review Committee Members]**
- b. Sign the filing checklist or memo; send for supervisory review and concurrence. **[Review Committee Members]**
- c. Perform a secondary review of the signed checklist to determine concurrence on the fileability, rationale, and any letter ready comments. Any non-concurrence must be accompanied by a written explanation. **[Branch/Lab Chief, Division Director]**
- d. Prepare a written justification, if the reviewer's recommendation is not accepted, enter into the appropriate regulatory system. **[Branch/Lab Chief, Division Director]**
- e. Certify the filing checklist or memo after secondary review is completed, enter into the appropriate regulatory system. **[Review Committee Members]**

3. After Filing Meeting – Meeting Summary and RTF Letter

- a. Draft the Filing Meeting Summary and document the final decision. The final decision should include the rationale for not filing the submission and a list of missing, incomplete, or inaccessible information. **[RPM/Chair]**
- b. Draft the Refuse to File letter using the current CBER letter template. Please refer to CBER's Review Letter Templates on CBER's Intranet Web page for the most recent approved template. Include the following: **[RPM]**
 - i. The deficiencies that form the basis for the RTF decision.
 - ii. The option to protest the Agency's decision and request that CBER file and review the application over protest (FOP), as well as a web site link to *SOPP 8404.1: Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File Over Protest)*.
- c. Send draft Filing Meeting Summary and RTF Letter to Review Committee Members, Branch/Lab Chief, Division Directors and Office Directors for concurrence. **[RPM]**
- d. Review Filing Meeting Summary and RTF Letter for accuracy and completeness and provide feedback to RPM. **[Review Committee Members, Branch/Lab Chief, Division Directors, Office Directors]**
- e. Obtain concurrence of Filing Meeting Summary and RTF Letter. Signature authority for RTF Letter is the Office Director or designee. **[RPM]**
- f. Enter signed and certified Filing Meeting Summary and RTF Letter into the appropriate regulatory system. **[RPM]**
- g. Ensure that the RTF letter is mailed to the applicant within 60 days of the CBER receipt date. **[RPM]**
- h. Follow *DCC Procedure Guide #8 Procedure for Filing Final Action Packages Containing FDA Correspondence For Marketing Applications* or *DCC Procedure Guide #23 Procedure for Filing Final Action Packages Containing Electronic FDA Communication for Marketing Applications* as applicable to complete the final action package processing. **[RPM, Review Committee Members]**

B. Manufacturing Supplements

1. Review submission for completeness and adequacy of contents and potential refuse to file issues before day 30. **[Review Committee Members]**
2. Notify the Chair, RPM, supervisors (Branch/Lab Chief, Division Director) and the ADRM of the potential of a RTF recommendation. **[Review Committee Members]**
3. Determine whether the submission should or should not be filed. **[Review Committee Members, Branch/Lab Chief, Division Director, Office Director, ADRM]**
4. If a RTF decision is made, document the RTF issue(s) in a memorandum which includes the rationale and a list of missing, incomplete, or inaccessible information. **[Review Committee Members]**

Note: if the decision is to file the supplement, refer to *SOPP 8401.2: Administrative Processing of BLAs and NDA Supplements* for filing procedures.

5. Sign and send the memorandum for supervisory review and concurrence. Upload the memorandum into the appropriate system. **[Review Committee Members]**
6. Draft the Refuse to File letter using the current CBER letter template. Please refer to CBER's Review Letter Templates on CBER's Intranet Web page for the most recent approved template. Include the following: **[RPM]**
 - a. The deficiencies that form the basis for the RTF decision.
 - b. The option to protest the Agency's decision and request that CBER file and review the application over protest (FOP), as well as a web site link to *SOPP 8404.1: Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File Over Protest)*.
7. Send RTF Letter to Review Committee Members, Branch/Lab Chief, Division Directors and Office Directors for concurrence. **[RPM]**
8. Review RTF Letter for accuracy and completeness and provide feedback to RPM. **[Review Committee Members, Branch/Lab Chief, Division Directors, Office Directors]**
9. Obtain concurrence of RTF Letter. Signature authority for RTF Letter is the Office Director or designee. **[RPM]**

10. Enter and upload the RTF Letter into the appropriate system. **[RPM]**
11. Ensure that the RTF letter is mailed to the applicant within 60 days of the CBER receipt date. **[RPM]**
12. Follow *DCC Procedure Guide #8 Procedure for Filing Final Action Packages Containing FDA Correspondence For Marketing Applications* or *DCC Procedure Guide #23 Procedure for Filing Final Action Packages Containing Electronic FDA Communication for Marketing Applications* as applicable to complete the final action package processing. **[RPM, Review Committee Members]**

VIII. Appendices

A. [Appendix A: Refusal to File \(RTF\) versus Complete Review](#)

IX. References

A. References below are CBER Internal:

1. JA 910.06: Completing a Filing Review
2. DCC Procedure Guide #8: Procedure for Filing Final Action Packages Containing FDA Correspondence For Marketing Applications
3. DCC Procedure Guide #23: Procedure for Filing Final Action Packages Containing Electronic FDA Communication for Marketing Applications

B. References below can be found on the Internet:

1. [Guidance for Industry: Providing Regulatory Submissions in Electronic Format: Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications](#)
2. [SOPP 8401: Administrative Processing of Original Biologics License Applications \(BLA\) and New Drug Applications \(NDA\)](#)
3. [SOPP 8401.2: Administrative Processing of BLAs and NDAs Supplements](#)
4. [SOPP 8404.1: Procedures for Filing an Application When the Applicant Protests a Refusal to File Action \(File over Protest\)](#)

X. History

Written/Revised	Approved	Approval Date	Version Number	Comment
Martha Monser	N/A	December 11, 202	9	Technical Update: Replace "database" with "system"
Martha Monser	N/A (Reviewed by Job Aid Coordinator)	January 6, 2020	8	Technical Update: new format/font and corrections to reference titles and URLs

Written/Revised	Approved	Approval Date	Version Number	Comment
Martha Monser	Christopher Joneckis, PhD	March 11, 2018	7	Update for consistency with electronic filing requirements and to include manufacturing supplements
Martha Monser	Christopher Joneckis, PhD	September 1, 2017	6	Technical Update for PDUFA VI and removal of previous Appendix A (FR 38771 notice)
Linda Dixon	Christopher Joneckis, PhD	January 17, 2017	5	Updated for consistency with JA 910.06
Sandra Menzies	Christopher Joneckis, PhD	July 2, 2015	4	Update to use Filing Checklists to support RTF
RMCC/Lydia Falk	Robert A. Yetter, PhD	August 22, 2007	3	Corrects link to CBER's RTF philosophy as per Federal Register notice (#38771)
Leonard Wilson	Robert A. Yetter, PhD	October 2, 2002	2	Clarifies roles and responsibilities, adds reference to FOP procedures.
CBER Application Policy Task Force	Michael Beatrice	November 1, 1993	1	Reissued as SOPP 8404 in August 1997. No change to Guide Content (OD-R-2-93)

SOPP 8404 Appendix A: Refusal to File (RTF) versus Complete Review

In general, an RTF is based on omissions of clearly necessary information (e.g., information required under the statute or regulations) or omissions or inadequacies so severe as to render the application incomplete on its face and where the omissions or inadequacies are obvious, at least once identified, and not a matter of interpretation or judgment about the meaning of data submitted.

An RTF:

1. Is not a final determination concerning potential approvability; it can be an early opportunity for the applicant to develop a complete application, but will delay, at least for a time, a full review of the application.
2. Is not necessarily a final decision regarding the scientific/medical merits of the application; instead, it is an early signal to the applicant that the application has omissions or inadequacies so severe as to render the application incomplete on its face or to introduce significant impediments to a prompt and meaningful review (e.g., the need for substantial amounts of additional data and analyses). This message is transmitted early so that "repairs" can be promptly initiated by the applicant.
3. Can be made if the applicant submission is based on a study or studies deemed inadequate during the Investigational New Drug (IND) review process and which remain uncorrected after the inadequacies were clearly communicated to the applicant by CBER.
4. May apply if the application contains other uncorrected deficiencies (e.g., manufacturing or product specifications) which were clearly communicated to the applicant before submission of the application sufficient to require resolution before a meaningful review could occur.
5. Is not an appropriate vehicle for dealing with complex issues and close judgments on such matters as balancing risks and benefits, magnitude of clinical effect, acceptability of a plausible surrogate marker, or nuances of study design (although inadequate designs may lead to RTF, see below).

By contrast, issuance of a Complete Response (CR) Letter (after a complete review) is generally based on critical omissions of data or analyses as well as on an adverse judgment about the data, conclusions, rationale, etc., presented in the application.

For example, a Complete Response Letter could be issued based on the conclusion that:

1. Effectiveness has not been demonstrated,
2. An analysis was incorrectly carried out,
3. Clinical trials were poorly designed or conducted,
4. Safety has not been adequately demonstrated, or

5. Outstanding compliance issues remain.

These judgments would not serve as the basis for RTF unless the deficiencies were so severe as to render the application incomplete on its face.

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