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. CBER believes an RTF action can allow an applicant to address critical insufficiencies that do not permit a substantive review and to submit a complete new BLA that may permit a substantive 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 or memos, if there is not a checklist, 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.

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 may be made based on findings such as:

1. Administrative incompleteness, e.g., 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, including clinical information, quality, manufacturing, and facility information, pharmacology/toxicology information and/or critical statistical analyses or the analysis of a study as planned in the protocol (as opposed to a different, post-hoc analysis).

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.

B. 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. Failure to submit agreed-upon minor components within 30 days will be subject to an RTF decision.

C. CBER's initial decision on whether 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. CBER will attempt to rectify easily correctable deficiencies (refer to Appendix A for examples).

D. When an RTF is recommended by the review committee and before a final decision, internal discussions with senior Center leadership will be held to include the Office Director from the relevant review office with signatory authority for the letter, CBER's Associate Director for Review Management, CBER's Associate Director for Policy, the Center Director and Deputy Center Director. Refer to *Job Aid (JA) 910.22: Procedures for Upper Center Management Leadership Briefing Before Issuing a Refuse-to-File Letter*.

E. An RTF is not a final determination concerning potential approvability or 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. It is an opportunity for the applicant to develop a complete, new submission.

F. RTF deficiencies are distinct from complete response (CR) deficiencies. CR deficiencies apply when a complete review of a filed application indicates that there are deficiencies that preclude the approval of the application based on the information provided at that time, e.g., balancing risks and benefits, magnitude of clinical effect, acceptability of a plausible surrogate marker, or nuances of study design.

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 – The Signatory Authority who signs RTF letters. Writes separate memo for a non-concurrence.

D. Review Committee Member – Reviews submission, recommends whether or not the submission can be filed, documents recommendation in the filing

checklist or memo, discusses the filing recommendation with management, reviews draft meeting summary and draft Filing or RTF letter.

VII. Procedures

A. Original BLAs, NDAs and Efficacy Supplements

1. Before the Filing Meeting

a. Review the submission as described in *JA 910.06: Completing a Filing Review.* **[Review Committee Members]**

b. Ensure that the RTF briefing meeting has been scheduled as described in *JA 910.22: Procedures for Upper Center Management Leadership Briefing Before Issuing a Refuse-to-File (RTF) Letter*. **[RPM]**

c. Notify the Chair, RPM, and supervisors (Branch/Lab Chief, Division Director) of the potential for an RTF recommendation, if applicable. **[Review Committee Members]**

d. Draft and distribute the Filing Meeting Agenda in preparation for the Filing meeting. **[RPM]**

Note: Ensure CBER's Associate Director for Review Management (ADRM) and upper office management (division, office directors as appropriate to the issue) are invited if there are significant review or potential RTF issues. (Refer to *R 910.02: Attendee Table for BLA/NDA Meetings* for complete list of recommended attendees).

e. Ensure that upper office management (i.e., Division Directors, Office Director) is notified immediately upon discovering that an RTF recommendation might be made. **[Chair/RPM]**

f. Complete the filing checklists or memo, summarize all potential review deficiencies and RTF items in letter ready format in the appropriate section of the checklist or memo. **[Review Committee Members]**

g. Email the checklists or memo, with the appropriate management copied, to the Chair and RPM before the filing meeting. **[Review Committee Members]**

h. 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, CBER ADRM]**

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/Memos

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 deficiencies. **[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 or memo to determine concurrence on the filing decision, rationale, and any letter ready comments. **[Branch/Lab Chief, Division Director]** Note: any non-concurrence must be accompanied by a written explanation/memo and included in the administrative file per standard procedures.

d. Upload the filing checklist or memo after secondary review is completed into the appropriate regulatory system through CBER Connect. **[Review Committee Members]**

3. After Filing Meeting - Meeting Summary/RTF Letter

a. Draft the Filing Meeting Summary and document the recommendation which should include the rationale for not filing the submission and a list of deficiencies. **[RPM/Chair]**

b. If an RTF is recommended, ensure that the Office Director from the relevant review office with signatory authority for the letter, CBER's ADRM, CBER's Associate Director for Policy, the Center Director and Deputy Center Director are briefed on the recommendation. Refer to *JA 910.22: Procedures for Upper Center Management Leadership Briefing Before Issuing a Refuse-to-File (RTF) Letter* for procedures and *R 910.02: Attendee Table for BLA/NDA Meetings* for complete list of recommended attendees. **[RPM]**

c. Draft the Refuse to File letter using the current CBER letter template (refer to CBER's Review Letter Templates in ORO's SharePoint Online (SPO) library 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)*.

d. Send draft Filing Meeting Summary and RTF Letter to Review Committee Members, Branch/Lab Chief, Division Directors and Office Directors for concurrence. **[RPM]**

e. 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]**

f. Obtain concurrence on the Filing Meeting Summary and RTF Letter. The signature authority for RTF Letter is the Office Director or designee. **[RPM]**

g. Enter Filing Meeting Summary and RTF Letter into the appropriate regulatory system through CBER Connect. **[RPM]**

h. Ensure that the RTF letter is sent to the applicant within 60 days of the CBER receipt date. **[RPM]**

i. 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, Office Director) of the potential of an 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]**

4. If an RTF decision is made, document the RTF issue(s) in a memorandum which includes the rationale and the list of deficiencies. **[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. Notify CBER's ADRM when an RTF decision has been made. [RPM]

6. Sign and send the memorandum for supervisory review and concurrence. Upload the memorandum into the appropriate regulatory system through CBER Connect. **[Review Committee Members]**

   Note: any supervisory non-concurrence must be accompanied by a written explanation/memo and included in the administrative file per standard procedures.

7. Draft the RTF letter using the current CBER letter template (refer to CBER's Review Letter Templates in ORO's SPO library 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)*.

8. Send RTF Letter to Review Committee Members, Branch/Lab Chief, Division Directors, and Office Directors for concurrence. **[RPM]**

9. Review RTF Letter for accuracy and completeness and provide feedback to RPM. **[Review Committee Members, Branch/Lab Chief, Division Directors, Office Directors]**

10. Obtain concurrence on the RTF Letter. The signature authority for RTF Letter is the Office Director or designee. **[RPM]**

11. Enter and upload the RTF Letter into the appropriate regulatory system through CBER Connect. **[RPM]**

12. Ensure that the RTF letter is sent to the applicant within 60 days of the CBER receipt date. **[RPM]**

13. 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. Appendix

A. SOPP 8404 Appendix A*:* Examples of Easily Correctable Deficiencies

IX. References

A. References below are CBER Internal:

1. JA 910.06: Completing a Filing Review

2. JA 910.22: Procedures for Upper Center Management Leadership Briefing Before Issuing a Refuse-to-File (RTF) Letter

3. R 910.02: Attendee Table for BLA/NDA Meetings

4. DCC Procedure Guide #8: Procedure for Filing Final Action Packages Containing FDA Correspondence For Marketing Applications

5. 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
Iliana Valencia	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	August 29th, 2024	11	Updated RTF examples under policy; incorporated policy from previous Appendix A into Policy section and updated appendix A to list examples of easily correctible deficiencies; minor clarifications in procedures; minor formatting editing.
Martha Monser	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	September 22, 2023	10	Updated to include an Upper Center Management briefing if a RTF is recommended.
Martha Monser	N/A	December 11, 2022	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
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.

Written/Revised	Approved	Approval Date	Version Number	Comment
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*:* Examples of Easily Correctable Deficiencies

This appendix provides examples of potentially easily correctible deficiencies. Although a single deficiency on this list may be easily correctable, a combination of these deficiencies may indicate an incomplete application and may be subject to refuse to file.

1. Electronic navigational problems.
2. Electronic non-compatibility or readability with the FDA's system.
3. Incomplete or missing Form FDA 356h (Application to Market a New or Abbreviated New Drug or Biologic for Human Use).
4. Incomplete electronic dataset(s) or missing components and technical issues or missing key components on datasets.
5. Missing financial disclosure statement on From FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and/or From FDA 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators).
6. Small amounts of missing data (e.g., collected but not submitted).
7. Failure to submit the content of labeling in electronic structure product labeling (SPL) format as described in 21 CFR 314.50(1)(1)(i) for NDAs and supplements and 21 CRF 601.14(b) for BLAs and supplements.
8. For NDAs, missing right of reference to information required for an application.
9. For NDAs, an incorrectly worded Debarment Certification statement.

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