SOPP 8404.1: Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File Over Protest)

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for the Center for Biologics Evaluation and Research (CBER) staff to describe the policies and procedures to be followed when an applicant disagrees with a Refuse to File (RTF) action and requests that CBER file the application over protest.

II. Scope

This SOPP applies to New Molecular Entity (NME), New Drug Application (NDA), original Biologics License Application (BLA) submissions, and associated efficacy or manufacturing supplements including those subject to the Prescription Drug User Fee Act (PDUFA), Biosimilar User Fee Act (BsUFA), and non-PDUFA products.

III. Background

A. To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, a manufacturer must submit an application to CBER as per 21 CFR 601.2. Applications are expected to be complete when

received by the Agency. Incomplete applications will be subject to an RTF decision. Within 60 days of receipt, CBER will review the application and will determine whether it meets the standards established to initiate a meaningful review (see *SOPP 8404: Refusal to File Procedures, Appendix A*). If the submission does not meet those standards, then, in accordance with SOPP 8404, CBER will notify the applicant that FDA refuses to file the application and refund 75% of the user fee payment (if a user fee is applicable). An RTF letter by the Agency notifies the applicant that (a) major deficiency(ies) exist(s) in the application.

B. An applicant may disagree with the CBER RTF decision and request a meeting to further discuss why the application was not filed. After the discussion, the applicant may still disagree with CBER's decision and accordingly request that CBER file and review the application over protest. In such cases, CBER will file and review the application.

IV. Definitions

A. File Over Protest – A request by an applicant to the Agency to file their application even though a refuse to file action on their application has been taken by the Agency.

V. Policy

A. When an applicant disagrees with an RTF decision by CBER, the applicant will be given the opportunity to discuss the deficiencies with CBER at a meeting. A request for a meeting may be submitted as an amendment to the original BLA within 30 days of the date of the refusal to file letter to discuss the reasons for the RTF. A meeting requested after 30 days may not be honored. Such meeting requests are granted and are generally considered to be a Type A meeting in accordance with *SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products*. Subsequent to the meeting, if within 30 days the applicant requests (via an amendment to the BLA) that FDA file the application, CBER will file the application over protest.

B. CBER will not file an application when a request to file the application is received more than 30 days after the meeting. The applicant will be notified in writing (via mail, fax, or secure email) that the request has been denied.

C. The filing of the application over protest will be regarded by CBER as a new original application for user fee purposes. When the RTF is issued, the applicant receives a 75% refund on the initial user fee paid if it was subject to a user fee. Upon filing over protest, the applicant must pay a new application user fee unless orphan designated or otherwise waived, e.g., small business waiver.

D. If an application is filed over protest, the suspended review clock will resume from the date which CBER received the request to file the application over

protest (providing the user fee accompanies the request as the application will be considered a new original application for user fee purposes, and the applicant must remit a new application fee, unless orphan designated or otherwise waived). Applications filed over protest will be reviewed on a standard clock.[1]

E. The application will not be eligible for the other parameters of the PDUFA/BsUFA Program, e.g., mid-cycle communication, late-cycle meeting.

F. CBER generally will not review amendments submitted to the application during any review cycle. CBER also generally will not issue information requests to the applicant during the agency's review.

G. The PDUFA VII resubmission goals will NOT apply to any class 1 or class 2 resubmission of the application following a CBER complete response action. Any such resubmission will be reviewed as available resources permit.

H. The BsUFA III resubmission goals will not apply to any resubmission of the application following a CBER complete response action. Any such resubmission will be reviewed as available resources permit.

VI. Responsibilities

A. Office Director – the Signatory Authority who signs RTF letters and the letter filing the application over protest.

B. Review Committee Members – Participates in the file over protest meeting and subsequent review activities.

C. Regulatory Project Manager (RPM) – performs all administrative actions associated with the processing of a request to file over protest.

VII. Procedures

A. Process meeting request and hold meeting (per *SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products*) if requested by applicant. **[RPM, Review Committee Members and Office Director]**

1. Inform applicant (and record in the meeting minutes) that if they plan to request that CBER file the application over protest, then the request needs to be submitted as an amendment to the BLA within 30 days of the meeting and any applicable user fees must be paid. **[RPM]**

[1] See Appendix 1 in the Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics

B. If an FOP request is submitted to the BLA within 30 days following the meeting, along with any applicable user fees, file the application over protest and notify the applicant, using the appropriate letter template, that the application is filed. **[RPM]**

C. Ensure all communications are entered into the appropriate regulatory system through CBER Connect. **[RPM]**

D. Contact RIB to have the application status changed from "refused to file" to "filed," and the dates and schedule reset, ensuring that the review schedule is "standard" in the appropriate system. **[RPM] Note**: The History of the RTF action will be retained in the Detailed Summary field.

VIII. Appendix

N/A

IX. References

A. References below are CBER Internal:

1. CBER's Letter Template Library

B. References below can be found on the Internet:

1. SOPP 8404: Refusal to File Procedures
2. SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products

X. History

Written/Revised	Approved By	Approval Date	Version Number	Comment
M.Monser	Sonday Kelly, MS, PMP, RAC Director DROP/ORO	September 7, 2023	8	Removed reversing decision steps as any reconsideration is done through dispute resolution processes and clarified that FOP is applicable to efficacy and manufacturing supplements.

Written/Revised	Approved By	Approval Date	Version Number	Comment
M.Monser	Katie Rivers, Acting Chief, RABOB/DROP /ORO	February 27, 2023	7	Clarifies that request from applicant to file over protest should be submitted as an amendment to the BLA and review schedule will be standard. Clarified user fee info.
M.Monser	Katie Rivers, Acting Chief, RABOB/DROP /ORO	December 21, 2022	6	Clarifies that meeting request should be submitted as an amendment to the BLA.
M.Monser	N/A	February 27, 2022	5	Technical update for 2022 CBER reorganization
M.Monser	N/A	December 11, 2020	4	Technical Update: For retirement of the EDR and remove “database”
H. Balick M. Monser	Christopher Joneckis, Ph.D.	August 23, 2020	3	Updated for PDUFA VI, to include biosimilars and current processes
RMCC – LTS	Robert Yetter, PhD	January 2, 2004	2	Relocate associated letter
Leonard Wilson, RMCC	Robert Yetter, Ph.D.	October 2, 2002	1	Original