

SOPP 8405.1: Procedures for Resubmissions to an Application or Supplement

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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 the categorization and processing of a submission received in response to a “complete response” letter issued to an original application or supplement, i.e., a resubmission.

II. Scope

- A.** This SOPP covers Biologic License Applications (BLAs) and New Drug Applications (NDAs) and the associated efficacy, labeling and manufacturing supplements subject to the Prescription Drug User Fee Act (PDUFA), the Biosimilar User Fee Act (BSUFA), and resubmissions of applications for non-user fee products.
- B.** This SOPP does not apply to BLAs subject to the Medical Device User Fee Act (MDUFA) or Abbreviated New Drug Applications (ANDAs) subject to the Generic Drug User Fee Act (GDUFA).

- C. This SOPP does not apply to PDUFA applications that were filed over protest.

III. Background

- A. The 1992 Prescription Drug User Fee Act (PDUFA) set goals for resubmissions of original BLAs and NDAs only. Subsequent reauthorizations added Class 1 and Class 2 categories for original applications and efficacy supplements.
- B. The Patient Protection and Affordable Care Act (PPAC Act) signed into law in March 2010, amended the Public Health Service Act (PHS Act) to create an abbreviated approval pathway for biological products that are demonstrated to be “highly similar” (biosimilar) to or “interchangeable” with an FDA-approved biological product. These statutory provisions also may be referred to as the Biologics Price Competition and Innovation (BPCI) Act. The BSUFA of 2012 authorized fees and set goals for the review of biosimilar biological product applications, including resubmissions. The BSUFA commitment letter does not categorize resubmissions into classes.

IV. Definitions

- A. **Complete Response (CR) Letter:** a letter issued by FDA when the complete review indicates that there are deficiencies remaining that preclude the approval of the application at that time.
- B. **Resubmission** – A submission to an NDA, BLA, or efficacy supplement that purports to answer all the deficiencies that need to be addressed by the applicant before approval as set forth in the CR letter. Note: The adequacy or inadequacy of the response does not impact whether or not it is considered to be a complete response; it is a simple determination of the presence or absence of a response or justification. A resubmission restarts the review clock.
- C. **Class 1 Resubmission** - A resubmission submitted after a CR letter that includes one or more of the following items:
 1. Final printed labeling;
 2. Draft labeling;
 3. Safety updates submitted in the same format, including tabulations, as the original safety submissions with new data and changes highlighted (except when large amounts of new information including important new adverse experiences, not previously reported with the product, are presented in the resubmission);
 4. Stability updates to support provisional or final dating periods;

5. Commitments to perform Phase 4 studies, including proposals for such studies;
 6. Assay validation data;
 7. Final release testing on the last 1-2 lots used to support approval;
 8. A minor re-analysis of data previously submitted to the application (determined by CBER as fitting the Class 1 category);
 9. Other minor clarifying information (determined by CBER as fitting the Class 1 category) such as a response to the CR letter that included only compliance issues, stating that the applicant's compliance status has been updated to "acceptable" and requesting the clock be resumed for completion of review for the application or supplement; and/or
 10. Other specific items that may be added later as the Agency gains experience with the scheme and will be communicated via guidance documents to the industry.
- D. Class 2 Resubmission** - A resubmission that includes any other item not specified as a Class 1 item, including:
1. Any item that would require a presentation to an advisory committee.
 2. A new manufacturing facility(ies) or would warrant a follow-up assessment and/or inspection of manufacturing facility(ies).
 3. Any data other than minor assay validation.
 4. Any resubmission with large amounts of data such as data to support process performance qualification.

V. Policy

- A. The classification (Class 1 or Class 2) of the resubmission for a PDUFA application or efficacy supplement is based on the information contained in the resubmission.
- B. For PDUFA applications and efficacy supplements, the classification will be determined, and a letter will be issued to the applicant that acknowledges receipt of the resubmission, states the classification, and gives the goal date for the review. For resubmissions of labeling or manufacturing supplements, acknowledgement will be in the form of a letter, telecon, or secure email.
- C. CBER will review and act on Class 1 and Class 2 Resubmissions for PDUFA applications or efficacy supplements within the timeframes specified in the current PDUFA goal letter as follows:

1. Class 1 within 2 months of the receipt date.
2. Class 2 within 6 months of the receipt date.

Note: Resubmissions are not classified as major amendments but are considered a new review cycle. If an amendment is received at any point that is deemed to be major during this review cycle, the review clock will be extended by three months. Only one major amendment is allowed per review cycle (refer to SOPP 8402: *Designation of Amendments as Major*).

- D. An amendment received near or at the time a CR letter is issued may be considered part of the resubmission if the content is determined to be relevant to responding to the CR letter.
- E. CBER will review and act on resubmissions for biosimilar biological product original applications or supplements with clinical data within 6 months of the receipt date as specified in the current BSUFA goal letter. Biosimilar biological products do not have Class 1 or Class 2 designations.
- F. CBER will review and act on resubmissions for manufacturing and labeling supplements within the same timeframe as the initial review cycle for the supplement (excluding any extension due to a major amendment of the initial supplement). 21 CFR 314.110(b)(1)(iii) applies to NDA supplements; CBER will use these same timeframes for BLA supplements. Manufacturing supplement resubmissions and labeling supplement resubmissions are excluded from category (class) designations.
- G. The resubmission will be considered complete if the applicant responds to each question or issue in the CR letter. The quality of the response will be evaluated during the review. Some responses by the applicant may be inadequate and will need to be addressed once the review has begun.
- H. If the applicant fails to respond to each question or issue, the resubmission will be considered incomplete, and the review will not restart until a complete response to each question or issue is received. The applicant will be notified of the reasons for the deficiencies. A phone conversation or secure e-mail will suffice as a means of communication in this regard. If the deficiencies are complex, a letter may also be sent to the applicant. All email acknowledgements must comply with *SOPP 8119: Use of Email for Regulatory Communications*. All telecon acknowledgements must comply with *SOPP 8104: Documentation of Telephone Contacts with Regulated Industry*.
- I. This SOPP does not apply to PDUFA applications that were filed over protest as they are not subject to the Program timelines. Review after a CR will occur based on available resources.

- J. Non-user fee (non-PDUFA) products will be reviewed under CBER's Managed Review Process (MRP) adhering to the performance goal timeframes as resources permit. Non-user fee application resubmissions are excluded from category (class) designations.
- K. For fast track, breakthrough therapy, and/or regenerative medicine advanced therapy (RMAT)-designated products, the intent of increased meetings/interactions with sponsors is to expedite product development, which is expected to be complete once the marketing application has been received. No additional PDUFA program benefits are extended for resubmissions, including formal communication plans.
- L. Applicants should anticipate that the recommendations in the Draft *Guidance for Industry and Review Staff: Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications* will be followed including "communication between applicant representatives and the review division RPM is the most effective and timely mechanism for interaction."

VI. Responsibilities

A. Regulatory Project Manager (RPM)

1. Ensure data for all submissions is entered in the appropriate regulatory system, including assignment of third level STN, if appropriate.
2. Determine initially whether the resubmission is a Class 1 or Class 2 Resubmission if the applicant indicates a Complete Response (CR) for a PDUFA application or efficacy supplement.
3. Determine initially whether the submission is a complete response if the applicant indicates a complete response for a biosimilar biological product submission, non-user fee submission or any non-efficacy supplement.
4. Ensure the applicant is notified via letter (if issues are complex), telecon, or secure email when a submission is determined to be incomplete (and therefore not a resubmission). Ensure that the clock was not started and will not start until a complete response to the action letter is received.
5. Ensure a Resubmission Acknowledgement Letter indicating the new action due date is sent to the applicant stating the classification once the submission is determined to be a complete response to a CR letter for an original application or efficacy supplement.
6. Ensure labeling or manufacturing supplement resubmissions are acknowledged by letter, telecon, or secure email.

7. Ensure all communications are documented in the appropriate regulatory system and uploaded through CBER Connect.

B. Review Committee Member

1. Determine whether the resubmission contains responses to all deficiencies in the CR letter.
2. Confirm or change the initial determination that the resubmission is a Class 1 or Class 2 for a PDUFA application or efficacy supplement.
3. Complete the review and act on resubmissions of applications or supplements within the timeframes specified in the current PDUFA and BSUFA goals letters.

VII. Procedures

- A.** Perform cursory review of the resubmission to determine if it is a proposed complete response or incomplete response to a CR letter. **[RPM]**
- B.** Ensure data for all submissions is entered in the appropriate regulatory system, including assignment of third level STN if appropriate. **[RPM]** Note: if the applicant designates the submission as a complete response, the review clock is started.
- C.** Notify the review committee of receipt of a resubmission and forward to appropriate review committee members. **[RPM]**
- D.** Confer with review committee to make certain the response for a resubmission is complete. **[RPM]**
- E.** Determine if a resubmission is a complete or an incomplete response. **[Review Committee Members]** Note: The resubmission will be considered complete if the applicant responds to each question or issue in the CR letter. If the resubmission is determined to be complete, the adequacy of the response will be evaluated during the review.
- F.** If the resubmission is incomplete:
 1. Ensure the designation in the regulatory system is corrected to “Incomplete Response to CR letter” if the review team confirms that the submission did not address all issues identified in the CR letter. **[RPM]**
 - a.** The data entry in the regulatory system should reflect receipt of an Incomplete Response to CR letter rather than a complete response.
 - b.** When the information in the system is corrected, the review clock is re-set to reflect the original action close date.

2. Notify the applicant within 14 calendar days of receipt if the submission is determined to be an incomplete response via letter (if issues are complex), email, or telephone. **[RPM]**
 3. Ensure all communications are documented in the appropriate regulatory system and uploaded into CBER's electronic repository (CER). **[RPM]**
- G.** If the resubmission is complete:
1. Ensure the review clock was started upon receipt once the review team confirms that the resubmission is complete and the designation of "Response to CR letter" is selected in the regulatory system. **[RPM]**
 2. Determine initially whether the submission is a Class 1 or Class 2 Resubmission if the applicant indicates a complete response for a PDUFA application or efficacy supplement. Note: Class 1 or Class 2 designations do not apply to: manufacturing or labeling supplements, non-user fee or biosimilar biological products. **[RPM]**
 3. Confirm Class 1 or Class 2 category if the resubmission responds completely to an action letter for a PDUFA application or efficacy supplement. **[Review Committee Members]**
 4. Send a Resubmission Acknowledgement Letter for an original application or efficacy supplement within 14 calendar days of receipt, indicating the new goal date to the applicant. **[RPM]**
 5. Acknowledge a resubmission for a labeling or manufacturing supplement by letter, telecon, or secure email within 14 calendar days, indicating the new goal date. **[RPM]**
 6. Ensure all communications are documented in the appropriate regulatory system and uploaded into the CER. **[RPM]**
- H.** Continue review according to *SOPP 8401: Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA)* or *SOPP 8401.2: Administrative Processing of BLA and NDA Supplements*. **[Review Committee Members]** **NOTE:** A review of the filing checklists is recommended to ensure review continuity and completeness, particularly for files that may have been in CR status for an extended period.

VIII. Appendix

N/A

IX. References

- A.** References below are CBER internal:

1. CBER Letter Template SharePoint Online Library

B. References below may be found on the Internet:

1. [Biosimilar User Fee Act \(BSUFA\)](#)
2. [Prescription Drug User Fee Act \(PDUFA\)](#)
3. [Draft Guidance for Industry and Review Staff: Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications](#)
4. [SOPP 8104: Documentation of Telephone Contacts with Regulated Industry](#)
5. [SOPP 8119: Use of Email for Regulatory Communications](#)
6. [SOPP 8401: Administrative Processing of Original Biologics License Applications \(BLA\) and New Drug Applications \(NDA\)](#)
7. [SOPP 8401.2: Administrative Processing of BLA and NDA Supplements](#)

X. History

Written/Revised	Approved By	Approval Date	Version Number	Comment
Monser	Darlene Martin, MS, PMP ORO/DROP Director	November 13, 2022	8	Clarified expectations regarding expedited program designated products.
Monser	Darlene Martin, MS, PMP	November 1, 2021	7	Minor edit to remind reviewers to revisit filing checklists when review resumes. Added information on major amendments to policy and timeline for issuing notification if resubmission is not complete to procedures.
Monser	N/A	December 11, 2020	6	Technical Update for retirement of EDR and to replace "database" with "system"

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Coleman- Cheng	Chris Joneckis, Ph.D.	February 20, 2020	5	Revised to include PDUFA VI and Biosimilar reauthorization performance goals and procedures.
Dixon	Robert Yetter, PhD	Aug 14, 2012	4	Revised to include PDUFA V, Biosimilar and non-User Fee procedures
Dixon, Padgett, Wilson, Joneckis	Robert Yetter, Ph.D.	Feb 10, 2011	3	Revised for new format and to include manufacturing supplements and PDUFA IV reauthorization
Leonard Wilson	Robert Yetter, Ph.D.	Aug 30, 2002	2	PDUFA III changes
Rebecca Devine, Ph.D.	Rebecca Devine, Ph.D.	May 20, 1998	1	Original