

## SOPP 8402: Designation of Amendments as Major

**Version:** 9

**Effective Date:** September 22, 2023

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#### **I. Purpose**

This Standard Operating Policy and Procedure (SOPP) describes the policy and procedures for Center for Biologics Evaluation and Research (CBER) staff when assigning the designation of major amendment for Biologics License Applications (BLA)/Supplements or New Drug Applications (NDA)/Supplements and communicating to the applicant the designation and the effect of the designation on the goal date.

#### **II. Scope**

- A.** This SOPP covers Biologics License Applications (BLAs), New Drug Applications (NDAs), and associated efficacy and manufacturing supplements regulated under the Prescription Drug User Fee Act (PDUFA), biosimilar biological products regulated under the Biosimilar User Fee Act (BSUFA), and non-user fee submissions.
- B.** This SOPP does not apply to BLAs regulated under the Medical Device User Fee Act (MDUFA).

- C. This SOPP does not apply to ANDAs regulated under the Generic Drug User Fee Act (GDUFA) program.

### III. Background

- A. In commitments made in support of PDUFA and BSUFA, FDA agreed to the goal of complete reviews of BLAs, NDAs and their respective supplements and Biosimilar applications submitted under Section 351(k) of the PHS Act within specified time frames.
- B. During the first cycle, the division ordinarily reviews all amendments solicited by the Agency during the review, and any amendments to the application previously agreed upon (e.g., during the pre-NDA/BLA meeting). Substantial amendments submitted late in the review cycle may, however, be reviewed in a subsequent cycle, depending, in part, on other identified application deficiencies. The review division attempts to review all other amendments during the first review cycle, but may not be able to, or may decide not to do so in some instances (e.g., when the content of such an amendment does not address a known deficiency in the application).

### IV. Definitions

- A. **Amendment** – the submission of information to a pending application or supplement, including additional information or reanalysis of data previously submitted, to clarify, revise or modify the application/supplement as originally submitted.
- B. **Major Amendment** – an amendment to an original application, efficacy supplement, manufacturing supplement or resubmission of any of these applications, including biosimilars, that extends the review clock.
- C. **Unsolicited Amendment** – a submission of information or data not requested by the Agency.
- D. **Resubmission** – a complete response to an action letter addressing all identified deficiencies.
- E. **Class 1 resubmission** – applications submitted after a complete response letter that include the following items only or combinations of these 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 (postmarketing) 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 analysis of data previously submitted to the application (determined by the Agency as fitting the Class 1 category);
9. Other minor clarifying information (determined by the Agency as fitting the Class 1 category), and
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 industry.

An example of minor clarifying information could be a response to a CR letter that contained only compliance issues stating the applicant's compliance status has changed to acceptable and requesting the clock be started for completion of review for the application or supplement.

- F. Class 2 resubmission** – resubmissions that include any other items, including any items that would require presentation to an advisory committee or a re-inspection of facilities.

An example of a Class 2 resubmission could be one that includes a resubmission containing other than minor assay validation data.

## V. Policy

- A. All priority and standard license applications or supplements subject to user fee performance goals will be reviewed within established timeframes.
- B. Non-user fee products will be reviewed under CBER's Managed Review Process (MRP) adhering to the performance goal timeframes as resources permit.
- C. During the first cycle, the office ordinarily reviews all amendments solicited by the Agency during the review, and any amendments to the application previously agreed upon (e.g., during the pre-NDA/BLA meeting). Substantial amendments submitted late in the review cycle may, however, be reviewed in a subsequent cycle, depending, in part, on other identified application deficiencies. The review division attempts to review all other amendments during the first review cycle, but may not be able to, or may decide not to do so in some instances (e.g., when the content of such an amendment does not address a known deficiency in the application).
- D. Amendments will be assessed for the purpose of designation as major. **Note:** CBER determined that amendments received for Class 1 resubmissions,

undefined or labeling supplements will not be classified as major amendments.

- E.** Major amendments may contain one or more of the following:
- 1.** A substantial amount of new data not previously submitted to or reviewed by the Agency, such as a major new clinical safety/efficacy report, or a new complex or novel clinical protocol for a study that is required for full marketing approval such as a confirmatory trial for accelerated approval that includes real world evidence (RWE).
  - 2.** A major re-analysis of previously submitted study/studies.
  - 3.** Submission of a Risk Evaluation and Mitigation Strategy (REMS) with Element to Assure Safe Use (ETASU) not included in the original application or significant amendment to a previously submitted REMS with ETASU.
  - 4.** A substantial amount of new manufacturing or facility information not previously submitted to or reviewed by the Agency.
  - 5.** A new analysis of studies not previously submitted to the pending application or supplement.
- F.** The review clock will be extended for major amendments submitted to:
- 1.** Original applications and efficacy supplements:
    - a.** Major amendment may be submitted any time during the review cycle.
    - b.** Extends the goal date by three (3) months.
  - 2.** Manufacturing supplements:
    - a.** Major amendment may be submitted any time during the review cycle.
    - b.** Extends the goal date by two (2) months.
- G.** Only one major amendment is allowed per review cycle.
- H.** Unsolicited amendments to applications and supplements are discouraged; however, in some cases (e.g., new adverse reaction, safety information, manufacturing information, etc.) such amendments may be necessary.
- I.** Normally, unless the amount and type of information is substantive or voluminous, or the amendment is received so near the goal date as to preclude adequate time for the review, the review of a clarifying information request (IR) response will occur during the current review cycle. IR responses

do not extend the review clock without a designation as a major amendment. However, when appropriate (e.g., due to the nature, volume, or time of the submission) CBER may designate an IR response as a major amendment and extend the review clock.

- J. CBER will not usually review an unsolicited amendment after the review of the application or supplement is complete and the issuance of an action letter is imminent (i.e., the type of action letter has been decided and comments are being drafted).
  - 1. The receipt of these unsolicited amendments does not affect the goal date for the application or supplement. However, there may be cases, such as in a priority application, where the amendment may support an approval in that review cycle. In such cases the reviewing Office will determine whether the information should be considered prior to taking an action on the application.
  - 2. If unsolicited amendments are to be reviewed and meets the criteria for a major amendment, a designation of major should be made and the goal date revised accordingly.
  - 3. The decision to extend the review clock upon receipt of a major amendment is based on a variety of factors (e.g., content of the amendments, FDA workload and resources, existence of other known deficiencies that may affect approval and have not been addressed by the amendment), but the underlying principle is to consider the most efficient path toward completion of a comprehensive review that addresses application deficiencies and leads toward a first cycle approval when possible.

## **VI. Responsibilities**

### **A. Product Office Regulatory Project Manager (RPM)**

- 1. Ensure that review committee members are notified of amendments (in coordination with the Chair).
- 2. Ensure that potential major amendments are distributed to the review committee as soon as possible (in coordination with the Chair).
- 3. Consult the review committee, or other individuals as needed, to assign a designation of major to an amendment.
- 4. Ensure that the designation of amendments as major is made within 14 calendar days of receipt (or sooner if the action due date is less than 14 calendar days).

5. Update the appropriate regulatory system with the designation (the system will automatically extend the review clock).
6. Inform the review committee of new user fee related goal dates as appropriate.
7. Ensure that a letter is issued informing the applicant of the designation and changed user fee related goal dates if the submission is designated as a major amendment.

#### **B. Review Committee Members or Consultant**

1. Evaluate the amendment in accordance with the above definition and recommend, with justification, a designation of major amendment to the Chair and RPM, as appropriate.

#### **C. Review Committee Chair (Chair)**

1. Notify review committee of amendments received (in coordination with the RPM).
2. Distribute amendment to review committee (in coordination with the RPM).
3. Review and provide the final recommendation including a justification for designating the amendment as a major amendment to the Division Director or designee.

#### **D. Division Director or designee**

1. Agree or disagree with designation of major amendment.
2. Sign the Major Amendment Acknowledgement Letter

### **VII. Procedures**

- A.** Notify all review committee members that an amendment was received. **[RPM, Chair]**
- B.** Distribute submission to appropriate review committee members. **[RPM, Chair]**
- C.** Determine if the submission qualifies as a major amendment within 14 calendar days of receipt; notify Chair. **[Review Committee Member]**
- D.** Make recommendation, including the justification for designating the amendment as a major amendment to Division Director or designee. **[Chair]**
- E.** Agree or disagree with recommendation. **[Division Director]**

1. Notify Chair and RPM if there is disagreement with the recommendation **[Division Director]**
  2. Schedule meeting with review committee to resolve disagreements with the recommendation **[RPM]**
- F. If categorized as a major amendment:
1. Draft and send Major Amendment Acknowledgment Letter to applicant within seven (7) days after the decision is made; letter includes new goal date and the justification for accepting the amendment as a major amendment. Please refer to CBER's Letter Templates SharePoint Library for the most recently approved template. **[RPM]**
  2. Notify review committee of new review schedule. **[RPM/Chair]**
  3. Sign the Major Amendment Acknowledgment Letter **[Division Director]**
- G. Ensure all appropriate documentation is entered into the appropriate regulatory system through CBER Connect. **[RPM]**

### VIII. Appendix

N/A

### IX. References

A. References below are CBER internal:

1. CBER's Letter Templates SharePoint Library

B. References below can be found on the Internet.

1. [Prescription Drug User Fee Act \(PDUFA\)](#)
2. [PDUFA Performance Goals and Procedures Fiscal Years 2023 Through 2027](#)
3. [Biosimilar User Fee Act \(BSUFA\)](#)
4. [Biosimilar Biological Product Authorization Performance Goals and Procedures Fiscal Years 2023 Through 2027](#)

**X. History**

<b>Written/Revised</b>	<b>Approved By</b>	<b>Approval Date</b>	<b>Version Number</b>	<b>Comment</b>
Monser	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	September 22, 2023	9	Added additional items that could be considered MA per PDUFA commitment letter and CBER policy.
Monser	N/A	December 11, 2020	8	Technical revision for retirement of EDR and replacement of "database" with "system"
Monser	N/A (Reviewed by Job Aid Coordinator)	January 6, 2020	7	Technical Revision to current format/font, updated URLs in references and corrected location of Letter Templates
Monser	Carol Rehkopf	September 28, 2017	6	Technical revision for PDUFA VI and update for FDA's new visual identity requirements
L Dixon for RMCC	Christopher Joneckis, PhD	Aug 2, 2016	5	Revised to include change in procedures
L Dixon for RMCC	Robert A. Yetter, Ph.D.	Sept 19, 2012	4	Revised to include changes in PDUFA V and include Biosimilars
L Dixon for RMCC	Robert A. Yetter, Ph.D.	Feb 9, 2009	3	Incorporate changes based on current PDUFA agreement, performance goals
Gilliam B. Conley Len Wilson	Robert A. Yetter, Ph.D.	April 16, 2001	2	Updated to reflect policy changes: BLA replaces ELA & PLA; Major amendment option no longer available for supplements; Current milestone timeframes
Application Policy Task Force	Rebecca Devine	Aug 1, 1995	1	Reissued as SOPP 8402 in 11/21/1996. No change to Guide content. Formerly OD-R-7-96