SOPP 8402: Designation of Amendments as Major

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Table of Contents

I. Purpose 1
II. Scope 1
III. Background 2
IV. Definitions 2
V. Policy 2
VI. Responsibilities 4
VII. Procedures 5
VIII. References 6
IX. History 7

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).

III. Background

A. In commitments made in support of PDUFA and BsUFA, FDA agreed to the goal of complete reviews within specified time frames for Biological License applications (BLAs) submitted under section 351(a) of the PHS Act, New Drug applications (NDAs) submitted under section 505(b) of the FD&C Act, Biosimilar applications submitted under Section 351(k) of the PHS Act, and their respective supplements.

B. Good review management principles and practices have been established to ensure that the review process is managed in a consistent and efficient manner thereby decreasing the number of review cycles necessary for approval. Amendments to applications are important mechanisms to provide additional information and may vary considerably in their content affecting the time needed for a thorough review of the information.

C. Amendments may be designated as major as defined below. Amendments designated as major will change the review timeline.

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.

1. **Major Amendment –** an amendment to an original application, efficacy supplement, manufacturing supplement or resubmission[1] of any of these applications, including biosimilars, that extends the review clock.

2. **Unsolicited Amendment –** a submission of information or data not requested by the Agency.

V. Policy

A. Amendments will be assessed for the purpose of designation as major. When the goal date is extended by a major amendment, a letter will be issued to the applicant communicating the new goal date and the justification for classifying the amendment as major.

1. 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

[1] For the definition of a resubmission and policies and procedures for resubmissions, refer to SOPP 8405.1: Procedures for Resubmissions to an Application or Supplement available at: https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-procedures-sopps

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.

B. 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.

C. Only one major amendment is allowed per review cycle.

D. Major Amendments may be submitted any time during the review cycle and the review clock will be extended for:

1. Original applications and efficacy supplements (both standard and priority review schedules): extend the goal date by 3 months.

2. Manufacturing supplements: extend the goal date by 2 months.

E. The review of a clarifying information request (IR) response will occur during the current review cycle 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. 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.

F. Unsolicited amendments are discouraged. CBER will not 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. Exceptions may occur for example where new adverse reaction information, safety information, or manufacturing information submitted may support an approval in that review cycle.

2. If unsolicited amendments are to be reviewed and meet the criteria for a major amendment, a designation of major will be made and the goal date revised accordingly.

G. CBER's Associate Director for Review Management (ADRM) will be consulted before making a determination whether an amendment to an original application or efficacy supplement is major if the product or the proposed change, when approved, will have a major impact on improving public health (as evidenced by priority review designation, is receiving a priority review voucher, has orphan product status, etc.), has complex/controversial review issues, or has other extenuating factors, e.g., re-adjusting goal dates may impact other agencies (e.g., CDC, WHO, EU).

VI. Responsibilities

A. Product Office Regulatory Project Manager (RPM)

1. Ensures review committee members are notified of amendments (in coordination with the Chair).

2. Ensures potential major amendments are distributed to the review committee as soon as possible (in coordination with the Chair).

3. Consults the review committee, or other individuals as needed, to assign a designation of major to an amendment.

4. Ensures 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. Updates the appropriate regulatory system with the designation (the system will automatically extend the review clock).

6. Informs the review committee of new user fee related goal dates as appropriate.

7. Ensures a letter is issued informing the applicant of the designation and changed user fee related goal dates.

B. Review Committee Members or Consultant

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

C. Review Committee Chair (Chair)

1. Notifies the review committee of amendments received and distributes amendment to review committee (in coordination with the RPM).

2. Reviews and provides 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. Agrees or disagrees with designation of major amendment.

2. Signs the Major Amendment Acknowledgement Letter.

E. CBER ADRM

1. Agrees or disagrees with designation of major amendment to an original application or efficacy supplement that, when approved, will provide a major improvement to public health, there are complex and/or controversial associated review issues, or if approval timelines are extended will affect another agency.

VII. Procedures

A. Notify all review committee members that an amendment was received. **[RPM, Chair]**

B. Distribute amendment to appropriate review committee members. **[RPM, Chair]**

C. Determine if it qualifies as a major amendment within 14 calendar days of receipt; notify Chair and RPM. **[Review Committee Member]**

D. Make recommendation, including the justification for designating the amendment as a major amendment (MA) to Division Director or designee. **[Chair]**

E. Review recommendation and agree or disagree, considering impacts on public health if the due date is extended and whether there are other factors to consider (e.g., impact to other regulatory or health agencies). **[Division Director]**

1. Write a separate review memo, if there is disagreement with the recommendation, in accordance with internal procedures, and notify the Chair and RPM. **[Division Director]**

F. For original BLA, NDA, biosimilar, and efficacy supplements when extending the goal date may have a significant impact on public health or affect other agencies, notify the ADRM via email of the recommendation to designate an amendment as major. Include email and review memo with supervisory concurrence. **[RPM]**

G. Consider public health impact of MA, considering all factors and consulting with the Center Director, as appropriate, and make decision on designation. **[ADRM]**

1. If MA recommendation is not supported, follow procedures for a supervisory non-concurrence. **[ADRM]**

H. Notify RPM of decision via email. **[ADRM]**

I. Within 30 days of request (sooner if pending goal date is imminent) if it is categorized as a MA:

1. Draft acknowledgement letter. Refer to CBER's Review Letter Templates SharePoint Online Library for the most recently approved letter template. **[RPM]**

2. Sign the Major Amendment Acknowledgment Letter. **[Division Director]**

3. Issue Major Amendment Acknowledgment letter. **[RPM]**

4. Notify review committee of new review schedule. **[RPM/Chair]**

5. Ensure all documentation is included in the administrative file by uploading through CBER Connect into the appropriate regulatory system. **[RPM, Review Committee Members, ADRM]**

VIII. References

A. References below are CBER internal:

1. CBER's Review Letter Templates SharePoint Online Library

B. References below can be found on the Internet.

1. SOPP 8401: Administrative Processing of Original Biologic License Applications (BLA) and New Drug Applications (NDA)

2. SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Submissions
3. S-8405.1: Procedures for Resubmissions to an Application or Supplement
4. Prescription Drug User Fee Act (PDUFA)
5. 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

IX. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Valencia	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	October 10, 2024	10	Update to policy that ADRM to be consulted on original BLAs/NDAs and efficacy supplements in certain circumstances, updated throughout for clarity, updated to current procedures.
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

Written/ Revised	Approved By	Approval Date	Version Number	Comment
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