SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications, New Drug Applications and Supplements

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as an overview for reviewer's responsibilities for the Chemistry, Manufacturing and Controls (CMC) section of a Biologics License Application (BLA) or a New Drug Application (NDA) and their respective supplements for Center for Biologics Evaluation and Research (CBER) staff. Details regarding CMC reviewer's responsibilities are outlined in *C905.04: CMC Filing Review Checklist for BLA, NDA, and Efficacy Supplements*.

II. Scope

A. This SOPP applies to the CMC review responsibilities for Biologics License Applications (BLA), New Drug Applications (NDA) and related supplements.

B. This SOPP does not address review responsibilities for Premarket Approval Applications (PMAs), licensed (BLA) In Vitro Diagnostics

(IVDs) or blood and blood components intended for transfusion and for further manufacture that are reviewed by the Division of Blood Components and Devices (DBCD)/Office of Blood Research and Review (OBRR).

III. Background

This SOPP describes the overall review responsibilities for the CMC section for divisions in the product offices, the Division of Biological Standards and Quality Control (DBSQC)/Office of Compliance and Biologics Quality (OCBQ) and the Division of Manufacturing and Product Quality (DMPQ)/OCBQ, CBER's CMC Filing Checklist (*C 905.04: CMC Filing Review Checklist for BLA, NDA and Efficacy Supplements*) provides a detailed breakdown of the responsibilities. The checklist also serves as the initial review of the submission for completeness. If a section is listed as a responsibility in the checklist, the subsequent review memos should also contain a review and evaluation of the information by the designated review division. Some sections will be "optional" for one or more CBER divisions while other sections may be the primary or a shared responsibility for reviewers.

IV. Definitions

A. **Biotech product:** Biological product produced using DNA recombinant technology.

B. **Drug Substance:** Active ingredient intended to furnish effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body but does not include materials used in the productions of such ingredient. In the context of the CMC review, the production of the Drug Substance is covered in sections under 3.2.S up to the point before the final formulation.

C. **Drug product:** Finished dosage form containing an active drug ingredient generally, but not necessarily, in association with inactive ingredients (excipients). In the context of the CMC review, the production of the Drug Product covers all items listed under 3.2.P from the beginning with final formulation through final labeled product.

D. **Excipient:** An ingredient added intentionally to the drug substance, which should not have pharmacological properties in the quantity used (inactive ingredient). An excipient is part of drug product. Thus, in the context of the CMC review, the Drug Product section (3.2.P) also contains information on excipients.

V. Policy

A. The CMC section of a BLA, NDA or supplement will be reviewed by staff assigned as described in the *C 905.04: CMC Filing Review Checklist for BLA, NDA and Efficacy Supplements* checklist.

B. An IR communication may be issued to request further information, including a clarification that is needed to complete the discipline review of an original BLA or NDA and their respective amendments and supplements. IR communications should include the four essential components of Four-Part Harmony:

1. What was provided – acknowledgement of the information submitted by the applicant, including references to sections, page numbers, or tables where appropriate

2. What is the issue or deficiency – identification of a specific issue or concern with information that was submitted, is missing, or is inadequate

3. What is needed – explicit request for additional information needed to address the issue and potential alternate ways of satisfying the issue, if applicable

4. Why it is needed – statement of basis for the deficiency that includes:

a. Effect or impact of the specific issue or concern on the patient or marketing application decision, and

b. Specific reference[1] (when available, applicable and relevant)

Note: IR communications should not be sent late in the review cycle. See *SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Submissions*.

C. Product Office, DMPQ and DBSQC CMC reviewers will use CBER's CMC BLA review memorandum template (*T846.04: CBER CMC Review Memorandum*) to document their reviews of BLAs, NDAs and substantial Prior Approval Supplements (PAS). PAS that contain major CMC changes and require the evaluation of multiple electronic Common Technical Document (eCTD) sections of Module 3 are considered substantial. For example, PAS that propose changes to the drug substance manufacturing process are usually substantial

[1] A specific reference is an applicable section of a final rule, regulation or statute; applicable section of a final guidance; and/or applicable section of an FDA-recognized consensus standard (unless the entire or most of the rule, regulation, statute, or document is applicable).

because multiple sections of module 3.2.S.2. may need to be reviewed.

D. The review of BLAs for licensed IVDs and for blood and blood components intended for transfusion and for further manufacture (reviewed by the DBCD/OBRR) are excluded from the requirement to use the CMC review memorandum template.

E. The filing checklist also serves as the guide to the individual items that need to be addressed within the CMC review memo, if applicable for the submission (for example, if the supplement is for a fill and finish facility, there won't be a need to review a drug substance section as it wouldn't be submitted in the supplement).

F. Final review memos will include a recommendation for approval, a complete response or denial decision and be in the format described in the CBER CMC Review memo template.

VI. Responsibilities

A. Division of Manufacturing and Product Quality (DMPQ):

1. Reviews and evaluates BLA/NDA and supplement submissions to ensure the Chemistry, Manufacturing and Controls, as they relate to the establishment, facility, and equipment, meet the regulatory requirements for Current Good Manufacturing Practices for drug substance(s), drug product, intermediates, diluents and adjuvants.

2. Leads pre-license/pre-approval inspections for BLAs and supplements to ensure facilities and Quality Systems are adequate to support licensure or to continue manufacture of product(s) as licensed after changes have been submitted to the Agency.

3. Works with the review committee to determine when pre-approval inspections are necessary for NDAs and supplements.

B. Division of Biological Standards and Quality Control (DBSQC):

1. Reviews BLA, NDA and supplement submissions to ensure all Drug Substance and Drug Product release test methods as requested by the product office are suitable and properly validated.

2. Reviews lot release protocols and develops testing plans to be used for CBER lot release.

3. Conducts laboratory testing in support of the BLA review.

4. Performs confirmatory testing of submitted product samples to ensure biological products will be released according to licensed test methods and product specifications.

5. Manufactures and calibrates reference reagents to support approval of annual influenza virus vaccine strain change supplements.

6. Reviews original submissions and changes (not only analytical methods) to the manufacturing process for Limulus Amebocyte Lysate (LAL) products.

7. Reviews analytical procedures and their method validation/qualification for up-stream and material in-processing test methods.

C. Product Offices

1. Reviews and evaluates information submitted in the CMC section of BLA, NDA and supplements that relate to the manufacture, manufacturing controls, specification and stability for the drug substance, drug product, intermediates, diluents, and adjuvants as well as raw materials and excipients to ensure a safe and effective product.

2. Ensures that the manufacturing process is validated to reliably and reproducibly generate a quality product and limits/specifications chosen by the applicant are appropriate for determining the control over the process as well as demonstrating the quality of the product.

VII. Procedures

A. Complete the CMC filing checklist, *C 905.04: CMC Filing Review Checklist for BLA, NDA and Efficacy Supplements,* within the prescribed timeframes. Refer to *SOPP 8401: Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA)*, SOPP *8401.2: Administrative Processing of BLA and NDA Supplements* and *Job Aid 910.06: Completing a Filing Review* for more information. [Reviewers]

B. Ensure the timely completion of the CMC checklist. [Regulatory Project Manager, Supervisors]

C. Complete the CMC review using CMC review memorandum template, *T846.04: CBER CMC Review Memorandum,* within prescribed timeframes (refer to SOPPs 84o1 and 8401.2 for more information). [Reviewers]

VIII. Appendix

N/A

IX. References

A. References below are CBER Internal:

1. C 905.04: Chemistry, Manufacturing, and Control Filing Checklist
2. T 846.04: CBER CMC BLA Review Memorandum
3. Job Aid 910.06: Completing a Filing Review

B. References below can be found on the Internet:

1. SOPP 8401: Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA)
2. SOPP 8401.2: Administrative Processing of BLA and NDA Supplements

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Lynch	Darlene Martin, MS, PMP ORO/DROP Director (acting)	September 28, 2022	4	Updated for PDUFA VII Changes
Monser	N/A (Reviewed by Job Aid Coordinator)	January 6, 2020	3	Technical Revision to current format/font
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OCBQ	R.A. Yetter, PhD	April 8, 2005	1	Original