SOPP 8401.2: Administrative Processing of BLA and NDA Supplements

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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 on the administrative processing of supplements to Biologics License Application (BLAs) and New Drug Application (NDAs).

II. Scope

A. This SOPP applies to supplements processed by CBER including those subject to the Prescription Drug User Fee Act (PDUFA) and the Biosimilar User Fee Act (BsUFA).

B. This SOPP does not apply to supplements for medical device BLAs or those subject to the Generic Drug User Fee Act (GDUFA).

III. Background

A. Applicants inform the Food and Drug Administration (FDA) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, and labeling established in the approved license application. The submission type, either a supplement or an annual report, is based on the change's potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they relate to the safety or effectiveness of the product. This SOPP covers changes that are submitted in a supplement. For information regarding annual reports, refer to *SOPP 8411.1: Administrative Handling and Review of Annual Reports for Approved Biologics License Applications*.

B. Information in a supplement may include changes to a product based on chemistry, manufacturing, or controls data and bioequivalence, or other studies (e.g., safety and immunogenicity), that changes (1) the strength or concentration; (2) the manufacturing process, equipment, or facility; or (3) the formulation (e.g., different excipients).

IV. Definitions

A. Amendment – Information submitted to a pending submission, including additional information or reanalysis of data previously submitted to clarify, revise, or modify the application as originally submitted.

1. **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.

2. **Unsolicited Amendment** - A submission of information or data not requested by the Agency.

B. Complete Response (CR) Letter – A letter issued when the complete review indicates that there are deficiencies remaining that preclude the approval of the application or supplement at that time. **Note**: A CR letter stops the review clock. The CR letter will summarize all the deficiencies remaining, and, where appropriate, describe actions necessary to place the application in a condition for approval.

C. Day-74 (Deficiencies Identified) Letter – A letter notifying the applicant of issues identified during the filing review phase that were not communicated in the filing letter.

D. Digitally Image - To convert a source document into a binary format that may be processed electronically.

E. Filing Letter – A letter issued to notify the applicant that their submission has been filed and will be reviewed. **Note**: The filing letter also includes information stipulated by PDUFA and may contain any identified filing deficiencies.

F. Information Request (IR) Communication– A communication sent to an applicant during submission review to request further information or clarification that is needed or would be helpful to complete the review.

G. Letter Ready Comments - Written comments formulated by the reviewer(s) of a submission written sufficiently well (e.g., correct grammar, spelling, punctuation) to be readily included in a communication (not always a letter) to the applicant.

H. Primary Discipline Review – A written review containing a reviewer's assessment and recommendations of all assigned areas of the submission.

I. Priority Review – A reduced review schedule compared to a standard review schedule to potentially allow the product to reach the market faster.

J. Secondary Discipline Review - A review by the Division Director and by intervening supervisory (i.e., Branch or Laboratory Chief) or nonsupervisory (Team Lead) reviewers of the primary discipline review memo.

K. Standard Review – All non-priority applications are considered standard applications.

L. Supplement - A request to FDA to approve a change to an approved license application.

Note: the following supplement types are designated by the review office after careful preliminary review of the submission:

1. **Efficacy** –

   a. A supplement to an approved application proposing to make one or more related changes from among the following changes to product labeling:

   - Add or modify an indication or claim;
   - Revise the dose or dose regimen;
   - Provide for a new route of administration;
   - Make a comparative efficacy claim naming another drug product;
   - Significantly alter the intended patient population;
   - Provides for, or provides evidence of effectiveness necessary for, the traditional approval of a product originally approved under 21 CFR part 314, subpart H, or 21 CFR part 601, subpart E (accelerated approval);
   - Provides for, or provides evidence of effectiveness necessary for, the traditional approval of a product originally approved under 21 CFR part 314, subpart I, or 21 CFR part 601, subpart H (the animal rule); and/or
   - Incorporate other information based on at least one adequate and well-controlled clinical study.

   b. A manufacturing supplement to an approved application requiring data from at least one adequate and well-controlled clinical study for approval.

2. **Labeling** - A supplement to an approved application that contains labeling changes only.

3. **Manufacturing -** A supplement to an approved application which includes a change(s) to the manufacturing process, including product testing or changes to the facility(ies) involved in the manufacturing of the product (may include labeling changes as well). See the *Guidance for Industry: Chemistry, Manufacturing and Controls Changes to an Approved Application: Certain Biological Products* and *Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture)*.

   Supplement subtypes:

   a. **CBE 30 (Changes Being Effected - 30 Days) –** A manufacturing supplement submitted to report changes that have a ***moderate potential*** to have an adverse effect on the product's quality and require an applicant to report the change to the FDA in a supplement at least 30 days prior to the distribution of the product made using the change. (21 CFR 601.12(c))

      Note: CBE30 is **not** applicable to labeling supplements; they are classified as either PAS or CBE.

   b. **CBE (Changes Being Effected Immediately)**

      i. **Manufacturing supplements -** To report a change(s) that has substantial similarity with the type of change that ordinarily warrants a CBE supplement; a situation in which the applicant provides evidence that the change has been validated in accordance with an approved comparability protocol under 21 CFR 601.12(e) and 21 CFR 601.12(c).

      ii. **Labeling supplements –** To report a change(s) as described under 601.12(f). The supplement must identify the change being made and include necessary supporting data. The supplement should be plainly marked: "Special Labeling Supplement—Changes Being Effected."

   c. **PAS (Prior Approval Supplement)** – To report a change(s) that have a ***substantial potential*** to have an adverse effect on the product's quality (i.e., major changes in manufacturing or labeling). A PAS must be approved by FDA prior to distribution of the product manufactured using the change. (21 CFR 601.12(b))

V. Policy

A. The procedures in this SOPP are not inclusive of all detailed procedures to be used to process BLA and NDA supplements. This SOPP should be used in conjunction with the SOPPs, Job Aids (JA), templates and other documents listed in the References section.

B. Where available, CBER staff will use regulatory templates that have been developed and approved specifically for assigned areas of responsibility. Use of templates promotes consistency in the documentation of elements and enhances comprehensive reviews.

C. A signed FDA form 356h should be submitted with all supplements. This information aids in routing it to the appropriate division for processing. The person who signs the Form FDA 356h is presumed to have signatory authority for the company, and therefore should be considered an Authorized Official of the company when submitting a BLA or NDA supplement. Accordingly, the signatory of the supplement, or designee, should sign all amendments submitted to CBER.

D. Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j)) (Form FDA 3674) should be included with all applicable submissions. The applicant is to determine the relevance of the application/supplement for compliance with Title VIII of FDAAA and check the appropriate box on the form. The applicant should also indicate on the form the National Clinical Trial (NCT) number(s) that apply.

E. For supplements subject to PDUFA, the performance goals identified in the most current PDUFA goals letter are applicable.

F. For supplements subject to BsUFA, the performance goals identified in the most current BsUFA goals letter are applicable.

G. Non-PDUFA supplements are to be reviewed under CBER's Managed Review Process (MRP) adhering to performance goal timeframes as resources permit. However, some steps in the process do not apply to non-PDUFA supplements.

H. The supplement is expected to be complete per 21 CFR 601.2(a) and 21 CFR 314.

I. 21 CFR 25.15(a) requires that an environment assessment (EA) or a claim of categorical exclusion (CE) be included whenever an application is submitted to FDA, inclusive of supplements to an approved application. Refer to *Job Aid 910.20: Procedures for Environmental Assessments and Claims of Categorical Exclusion* for more information, including procedures for requesting either an EA or CE if one was not submitted.

J. Requirements for electronic submissions:

1. Under Section 745A(a) of the Federal Food, Drug and Cosmetic Act (FD&CA), applicants are required to submit information electronically in the appropriate FDA-supported formats (Electronic Common Technical Document (eCTD)) for certain BLAs, NDAs, and Abbreviated New Drug Applications (ANDAs) and supplements to these submission types with the exception of devices and blood and blood components, including source plasma submissions.

2. Submissions that are required to be eCTD compliant, but not submitted electronically and electronic submissions that are not in a format that FDA can process, review, and archive will not be filed; they will be rejected, unless exempted from these requirements.

3. Please see the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format: Certain Human Pharmaceutical Product Applications and Related*

Submissions using the eCTD Specifications, for complete eCTD requirements and exceptions for more information.

4. Submissions not required to be in eCTD format (e.g., submissions for blood and blood components) should be submitted as directed on the FDA's eSubmitter website (https://www.fda.gov/ForIndustry/FDAeSubmitter/default.htm).

K. In order for FDA to send regulatory communications via email, the email must be sent to a secure email partner, to allow FDA to digitally sign and the encrypt message. For further information regarding secure email, please refer to CBER's *SOPP 8119: Use of Email for Regulatory Communications*.

L. Formal submissions (e.g., new INDs, original BLAs, etc,), information that is unsolicited, or that FDA did not agree to receive related to pending applications are not to be transmitted via email. Any such emails will not be accepted or included in the administrative file, please refer to CBER's *SOPP 8119: Use of Email for Regulatory Communications*.

M. Efficacy and Prior Approval Manufacturing Supplements which are incomplete are subject to a refuse to file decision. Please refer to *SOPP 8404*: *Refusal to File Procedures* for additional information.

1. If a supplement is not filed by CBER (refer to *SOPP 8404: Refusal to File Procedures*), and the applicant does not request that the application be filed over protest or follow the procedures for filing over protest [refer to *SOPP 8404.1: Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File over Protest)*], no additional submissions can be made to that supplement; a new supplement must be submitted.

N. Review Timeline - the review clock begins on the CBER receipt date.

1. A major amendment to a manufacturing supplement submitted at any time during the review cycle may extend the goal date by two months.

2. A major amendment to an efficacy supplement submitted at any time during the review cycle may extend the goal date by three months.

3. During FDA's review of a supplement, if the Agency identifies a manufacturing facility that needs to be inspected and was not included in the comprehensive and readily located list, the goal date may be extended by three months.

4. Only one extension can be given per review cycle.

O. Supplements managed and chaired by the Division of Manufacturing and Product Quality (DMPQ) include:

1. Chemistry, Manufacturing, and Controls (CMC) supplements for facility and/or equipment changes (except testing facilities) that do not include manufacturing process changes;

2. CMC supplements regarding changes to sterility, endotoxin, and pyrogen tests for intermediates (does not include final bulk drug substance or changes in the manufacturing processes or materials tested);

3. CMC supplements for introduction of new products into multi-use facility areas; and

4. CMC supplements regarding new containers with regard to container-closure integrity.

P. Supplements managed by DMPQ and chaired by Division of Biological Standards and Quality Control (DBSQC) include:

1. CMC supplements regarding changes to sterility, endotoxin, and pyrogen test methods at the drug substance (DS) and drug product (DP) stages;

2. CMC supplements with DP or DS test method changes as requested by or in agreement with the product office; and

3. Any supplements for *Limulus amebocyte* Lysate (LAL) containing Endotoxin detection products.

Q. Supplements managed by the relevant product office include:

1. Efficacy supplements;

2. Labeling supplements;

3. CMC supplements having no facility/equipment changes;

4. CMC supplements which involve both changes to facility/equipment *and* manufacturing processes, e.g., scale-up. These supplements may be chaired by either a DMPQ (DMPQ would then perform the RPM functions) or product reviewer; and

5. CMC supplements regarding product test methods and new test facilities (except DS and DP sterility, endotoxin, pyrogen testing, and other tests as requested or agreed to with the product office).

R. Equivalent Methods:

1. Supplements submitted under Equivalent Methods (21 CFR 610.9), should be reviewed for acceptability *upon receipt*. This would include consultation with the Office of Compliance and Biologics Quality (OCBQ).

S. Filing:

1. Filing meetings are encouraged for efficacy and other complex supplements. Filing meetings for non-PDUFA products may occur as needed when the supplement is incomplete or other issues are identified by the review team.

2. Prior to the filing meeting, each reviewer is expected to complete a *discipline specific* filing review checklist or document in a review memorandum any potential issues with the supplement that could result in a refuse to file decision or be included in a Day-74 letter.

3. The *discipline specific* filing review checklist is used in place of a filing review memorandum, if a discipline specific filing review checklist exists.

4. The *discipline specific* filing review checklist must be entered into the appropriate system and uploaded through CBER Connect into the CBER Electronic Repository (CER).

5. The filing meeting summary must also be entered into the appropriate regulatory system and uploaded through CBER Connect by day 60.

6. Generally, if deficiencies have been identified during the filing review that are not refuse to file issues, they will be communicated in the filing letter at day 60 (efficacy supplements only).

T. Unsolicited amendments are discouraged; however, in some cases (e.g., new adverse reaction, safety information, manufacturing information, etc.) such amendments may be necessary.

U. Unsolicited amendments, including responses to issues identified in the filing letter and responses to a Day 74 letter (efficacy supplements only), will be reviewed in accordance with the underlying principle that the most efficient path toward completion of a comprehensive review that addresses deficiencies and leads toward a first cycle approval, when possible, will be considered and as resources permit. However, CBER will not usually review an unsolicited amendment after the review of the 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).

V. Mid-cycle Meeting (internal):

1. Mid-cycle meetings are encouraged for efficacy and other complex supplements.

2. By the Mid-cycle meeting, each reviewer is expected to document their review progress in assigned areas of responsibility in a primary discipline review memorandum that summarizes content, documents the reviewer's assessment, and identifies key issues identified to date.

3. At the Mid-cycle meeting each reviewer is expected to discuss key findings documented in the draft primary discipline review memorandum.

W. CBER staff will not discuss the pending regulatory status of a submission with the applicant while the submission is still under review. The regulatory action may only be discussed after the final decision is conveyed to the applicant**.**

X. All communications, including telephone calls and other informal communications, are to be continuously entered into the appropriate regulatory system in real time; all documents

should be uploaded through CBER Connect. All letters issued by CBER must use the most recent approved template.

Y. Defined dates used on CBER correspondence and entered into CBER systems are described in regulatory *JA 820.02: Dating of CBER Correspondence.* CBER correspondence includes letters, internal memoranda, meeting or telecon minutes, and internal or outgoing e-mails or facsimiles (fax).

Z. All CBER correspondence should be entered into the appropriate regulatory system prior to the final action (e.g., approval or withdrawal). After the final action is taken, additional applicant amendments will be allowed to the submission for 14 calendar days, and any changes to CBER communications/documents will be allowed for 30 calendar days. After these timeframes, a lockdown is initiated and no additional or revised documents may be added to the submission without approval. Refer to regulatory *JA 910.08: Lockdown of Applicant Submissions and CBER Correspondence for Marketing Submissions* for additional information.

VI. Responsibilities

A. Review Committee Chair (Chair) – discusses and assures resolution of scientific issues and associated regulatory interpretations in concert with management. Specific responsibilities include ensuring that all components of the supplement are properly assigned for review and bringing scientific issues to the attention of management and facilitating resolution and consensus. The chair works closely with the RPM in executing these duties. The Chair is a member of the review committee.

B. Division Director - the signatory authority who signs action letters and concurs or does not concur with the reviewer's assessments and recommendations.

C. Document Control Center (DCC) - processes all incoming submissions, including loading electronic applications into CER, routing paper applications, processing, jacketing and storing approved applications, and filling document/file requests.

D. Regulatory Project Manager (RPM) – responsible for the overall management of the review. Specific responsibilities include: scheduling review committee meetings and PeRC meetings (if applicable), ensuring regulatory and administrative actions are completed on time, notifying management when timelines are not met, reviewing assigned sections, performing quality control checks, capturing review committee communications, ensuring regulatory systems are updated, and ensuring the file is administratively complete. The RPM is a member of the review committee.

E. Review Committee Members – each member performs a review of all assigned components of submission, participates in review committee meetings, and documents the review by completing the appropriate documentation, including but not limited to, the appropriate Filing Review Checklist, a Discipline Review Memo; enters all appropriate documentation into the appropriate regulatory system and uploads through CBER Connect. This review should be scientifically sound and follow Good Review Management Principles and Practices.

F. Supervisors – ensures the overall content of reviews are appropriate, all administrative processing steps are completed, including data entry, and all deadlines are met. Reviews and approves employee's review documents and other submission documents per CBER policies and procedures.

VII. Procedures

A. General Information

1. Each step in the Procedures section is chronologically listed where practicable. It is permissible to accomplish steps out of sequence when appropriate. Some steps in the process will not apply to all supplement types.
2. Review assessment and its documentation start when the application is received and progresses throughout the review timeline, such that the primary discipline review is nearly complete, if not complete, by the target date in time for the Mid-cycle meeting.
3. Refer to *C 910.04: PDUFA Checklist for Original BLAs and Efficacy Supplements* for additional information on target due dates.

B. Receipt and Initial Processing

1. Receive, digitally image (if applicable), process and load into the CBER Electronic Repository (CER). Notify the appropriate Office through the load notification. **[DCC]**

2. Review the 356(h) to ensure the applicant's designation of the submission, the supplement type and subtype are accurate. **[RPM]**

   a. If CBER disagrees with the supplement subtype and is upgrading from CBE or CBE30 to a PAS, change the subtype in the appropriate system and specify the classification change and action due date in the Acknowledgment letter.

   b. If the supplement should have been submitted as an annual report, reclassify the supplement in the appropriate system and specify the classification change in the Downgrade to Annual Report letter.

   Note: changes to be reported in an annual report are changes in the labeling, product, production process, quality controls, equipment, facilities or responsible personnel that have ***minimal*** potential to have an adverse impact on the product's identity, purity, potency, strength or quality as they relate to its safety or efficacy.

3. Verify that all the sections of the supplement are present and consistent with the Table of Contents (TOC). Notify the applicant of inconsistencies. **[RPM]**

4. Verify that the supplement is not inappropriately bundled as per the *Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*. **[RPM]**

5. Ensure Form FDA 3674 (for clinical trials) was submitted, all information necessary was provided, and the information is included in the appropriate regulatory system. ***Efficacy supplements only***

   a. If the form was not submitted, contact the applicant to request it. **[RPM or designee]**

6. Enter all required data fields into the appropriate system, including the Short Summary. **[RPM]**

7. Enter applicable submission details in the STN Special Characteristics field, e.g., Orphan designation, Breakthrough Therapy, CDISC, etc. Add all that are applicable. In addition, enter the indication, dosage form and potency information into the appropriate system, as applicable. **[RPM]**

8. Ensure all relevant information pertaining to the applicant, regulatory contact and manufacturing facilities reflected in the appropriate system and on form 356h are correct. **[RPM]**

9. Check daily for incoming submissions containing standardized study data and, if present, follow *JA 900.18: Study Data Validation* to request that a CDISC format validation be performed. **[CBER Data Standards Representative]** ***Efficacy supplements only***

   a. After the validation report is available, schedule a study data meeting to discuss the data, including the validation with review team. Meeting attendees should include the Data Standards Representatives, review team members responsible for reviewing studies with standardized study data (e.g., clinical, statistical, pharm/tox), the Clinical Data Analyst if one is assigned, and the RPM. **[RPM]**

   b. If revisions/corrections are needed after the validation report is presented to reviewers, send an Information Request (IR) to the applicant and upload it through CBER Connect. **[RPM]**

   c. Check to ensure that the “CDISC” STN Characteristic was entered into the Submission Information screen. **[RPM]**

10. Determine if approval of an exception has been requested under the Equivalent Methods and Processes regulation (21 CFR 610.9), for licensed biologics that modify a particular test method or manufacturing process or that modify a condition under which the method/process is conducted. **[RPM]**

    a. Ensure the supplement contains a complete description of the reason for the modification or process change. **[RPM]**

    b. Send a request for review by email to OCBQ’s Division of Case Management (DCM), which includes the following. **[RPM]**

i. A short summary describing the problem,

ii. A statement determining that the applicant performed an investigation into the issue, and

iii. that the applicant established corrective and preventative action plans to address the issue(s).

c. Review the submission and provide a decision to the product office. **[DCM]**

i. If the decision is to grant the exception, DCM notifies the product office, sometimes providing recommendations, and the product office initiates the review.

ii. If the decision is to not grant the exception, DCM notifies the product office and provides the reasons for the denial.

iii. The product office informs the applicant that the Center will not approve its request based on the quality of product, safety of product or other issues. The applicant may then be issued a denial letter or withdraw the supplement.

11. Request reviewer assignment from appropriate supervisor(s) and/or triage group, including the following as applicable: **[RPM]**

a. Chair
b. Clinical Reviewer
c. Clinical Pharmacology Reviewer
d. Animal Pharmacology Reviewer
e. Toxicology Reviewer
f. Developmental Toxicology Reviewer
g. CMC Reviewer
h. OCBQ/DMPQ RPM
i. OCBQ/DMPQ Reviewer
j. OCBQ/DMPQ/PRB Reviewer
k. OBPV Clinical Data Analyst
l. OBPV Digital Health Technology (DHT) Reviewer
m. OBPV Real World Evidence (RWE) Reviewer
n. Statistical Reviewer of Clinical Data
o. Statistical Reviewer of Non-clinical Data
p. Postmarketing Safety Epidemiological Reviewer
q. OCBQ/APLB Promotional Reviewer
r. OCBQ/APLB PNR Reviewer
s. OCBQ/BIMO Reviewer
t. OCBQ/DBSQC or OVRR/DBPAP/LIB Reviewer
u. Consult Reviewer(s)
v. OCBQ/DMPQ/Lead Inspector
w. CMC Inspector

x. Package/Container Reviewer
y. Labeling Reviewer

12. Assign Review Committee Members. **[Supervisor]**

13. Notify or confirm with the RPM and assigned committee members that they are part of the review committee. **[Supervisor]**

14. Screen the supplement to confirm all consult reviews needed are identified and appropriate consult reviewers have been notified. **[RPM, Chair]**

15. Enter, or ensure all review committee members have been entered, into the appropriate system. **[RPM]** Note: when review committee members are assigned the submission is electronically sent to reviewers.

16. Begin review of the supplement:

a. Identify any potential issues found during a preliminary review, including identification of data sets submitted incorrectly or absent datasets, and

b. Ensure all files can properly open, including PDF, and study data files. If problems are noted, contact the RPM. **[Review Committee Members]**

17. Send an email to the DCC Data Abstraction Team with the name(s) of the product reviewer(s) assigned to review the animal biological, chemical component information, if applicable. Refer to *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements* for additional information. **[Chair]**

18. Determine if the supplement is subject to PREA. **[RPM/Clinical Reviewer]**

a. A supplement is subject to PREA when it includes:

i. An assessment/study that is in response to or fulfills a PREA PMR
ii. A new indication
iii. New dosing regimen (*any change in a single dose, maximum daily dose, or dosing interval*)
iv. New active ingredient (*including a new combination)*
v. New dosage form (*e.g., lyophilized powder to transdermal patch*)
vi. A new route of administration (*e.g., subcutaneous to intramuscular)*

b. If there are questions regarding whether a supplement is subject to PREA, contact the office representative on the CBER Pediatrics Working Group.

19. Evaluate the information disclosed under 21 CFR §54.4(a)(2) about each covered clinical study in the supplement to determine the impact of any disclosed financial interests on the reliability of the study. ***Efficacy supplements only*** **[Clinical Reviewer, RPM]**

20. Ensure that the supplement includes either an EA or a CE. Refer to *JA 910.20: Procedures for Environmental Assessments and Claims of Categorical Exclusion* for more information. **[RPM, Review Chair and/or CMC Reviewer]**

21. Issue an STN Acknowledgment letter to the applicant and upload through CBER Connect. **[RPM]**

a. Except for blood and blood component products, for supplements affecting multiple products, an STN is assigned for each product and the STN Acknowledgment letter lists each STN and product.

Note: Blood and blood components are a multi-product BLA, therefore all blood and blood components are reviewed under one STN per applicant. In most cases, a blood and blood component submission will be assigned one 2nd level STN regardless of how many blood components are included in the submission. In rare circumstances, the changes in the submission can be spun-off into a separate 2nd level STN.

b. The filing decision may be addressed in the acknowledgement letter for manufacturing and labeling supplements.

c. Efficacy supplements have a separate filing letter.

22. Establish/confirm a draft review schedule as appropriate, including: **[RPM, Chair]**

- First committee meeting
- Filing decision
- Refuse to File briefing (efficacy supplements only)
- Mid-cycle meeting
- Labeling meetings
- Other meetings as necessary

23. Schedule all review meetings using Microsoft Outlook, inviting all review committee members and supervisors as appropriate. **[RPM]**

C. First Committee Meeting

24. Ensure all review committee members are assigned as appropriate, including any consult reviewers if needed. **[Chair]**

25. Ensure all review committee members have a clear understanding of their review responsibilities. **[RPM, Chair]**

26. Ensure all review committee members have received the appropriate documents or electronic links. **[RPM]**

27. Draft and distribute agenda for the First Committee Meeting. (Use template:

T 910.15: First Committee Meeting Agenda/Summary) **[RPM]**

28. Conduct first committee meeting: **[Chair, RPM]**

a. Review and confirm the review schedule, including the review clock, i.e., standard or priority review. **[Review Committee Members]**

b. Review/confirm if Orphan drug designation was granted for the specific indication contained in the supplement. ***Efficacy supplements only*** **[RPM]**

c. Review/confirm if the supplement is subject to PREA and discuss the timeframe for scheduling a PeRC meeting. If the supplement is subject to PREA because it includes a new indication, etc., verify that the applicant has an Agreed Pediatric Study Plan (PsP) in place in accordance with the *Draft Guidance – Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans.* ***Efficacy supplements only*** **[Review Committee Members]**

d. Determine if an Advisory committee (AC) meeting is likely. **(*Efficacy supplements only*) [Review Committee Members]**

e. Document any potential issues found in the early review, categorized by discipline, including identification of data sets submitted incorrectly, problems encountered opening tables or absent data sets, failure to have an Agreed-upon PsP, etc. **[RPM]**

f. Discuss whether pre-license, pre-approval and/or BIMO inspections should be required. **[Review Committee Members]**

g. Document whether pre-license, pre-approval and/or BIMO inspections are necessary. **[RPM]**

h. Confirm date for the filing decision and discuss specific filing expectations. **[Chair, RPM]**

29. Draft and circulate first committee meeting summary and identify follow-up activities. **[RPM]**

30. Review and comment or concur on the first committee meeting summary. **[Review Committee Members]**

31. Collate revisions for the first committee meeting summary and send for signature. **[RPM]**

32. Sign the first committee meeting summary and send it to the RPM. **[Chair]**

33. Enter meeting summary/minutes into the appropriate system and upload through CBER Connect. **[RPM]**

D. Filing Decision/ Meeting

34. Perform review in preparation for filing decision, as applicable. Refer to and follow *SOPP 8404: Refusal to File Procedures* if a refuse to file (RTF) action is being considered. **[Review Committee Members]**

a. For efficacy supplements, use the appropriate discipline specific Filing Review Checklist and refer to *JA 910.06: Completing a Filing Review*.

b. For other supplements, if substantial review issues are found, document findings. For manufacturing supplements, if considering an RTF action, prepare a formal review memorandum. **[Review Committee Members]**

c. Alert the supervisory chain immediately upon discovering that a RTF recommendation may be made. **[Chair]**

35. Draft and distribute agenda for the filing meeting (efficacy supplements only) using template: *T 910.16: Filing Meeting Agenda/Summary*) **[RPM]**

36. Conduct the filing meeting (efficacy supplements only). Each reviewer is expected to have completed the *discipline specific* filing review checklist and be prepared to discuss the relevant content of the supplement and present an overview that includes: **[Chair, Review Committee Members]**

a. A description of any required data that is missing from the supplement;

b. Any substantive deficiencies or issues that potentially have significant impact on the ability to complete the review or approve the submission;

c. A decision on filing, deficiencies identified letter, or RTF;

d. APLB will comment on the existence\status of a Proprietary Name Review;

e. Propose whether changes reported in the supplement will require an on-site inspection and whether the facility(s) are ready for inspection;

f. Propose whether product is subject to lot release, surveillance or exempt from lot release;

g. A decision regarding standard or priority review status;

h. A decision on whether the supplement is subject to PREA and/or fulfills an outstanding PREA PMR;

i. A decision regarding need for an AC; and

j. Any updates since the first committee meeting on pre-approval/BIMO sites requiring inspection and whether the sites are ready or not.

37. Document the RTF decision, if applicable. Any recommendation for not filing the submission must include a list of missing, incomplete, or inaccessible information **[Chair, RPM]**

a. Finalize the Filing Meeting Agenda/Summary (efficacy supplements only) or review memorandum (manufacturing supplements) and obtain management concurrence.

b. If RTF is recommended for an efficacy supplement, ensure that the upper management briefing procedures are followed, refer *JA 910.22: Procedures for Upper Center Management Leadership Briefing Before Issuing a Refuse-to-File (RTF) Letter.*

c. Enter all documentation in the appropriate regulatory system and upload through CBER Connect.

d. Refer to *SOPP 8404* for additional procedures, including those on notifying the applicant.

38. Update the filing checklist or review memo, if needed, and obtain first level supervisor review and signature. **[RPM]**

39. Upload the filing checklist or review memo through CBER Connect. **Note**: enter the name of the specific review discipline in the Summary Text. **[Review Committee Members]**

40. Draft and circulate the filing meeting summary using *T 910.16: Filing Meeting Agenda/Summary* template (efficacy supplements only). For non-user fee products without a filing meeting, document the filing decision in a filing memorandum. **[Chair, RPM]**

41. Review and comment or concur on the Filing Meeting Summary (efficacy supplements only). **[Review Committee Members]**

42. Collate revisions for the Filing Meeting Summary and send it for signature (efficacy supplements only). **[RPM]**

43. Sign the Filing Meeting Summary and send it to the RPM (efficacy supplements only). **[Chair]**

44. Enter the filing meeting date or filing memorandum date into the appropriate system. **[RPM]**

45. Upload the Filing Meeting Summary through CBER Connect (efficacy supplements only). **[RPM]**

46. Continue the Primary Discipline Review. **[Review Committee Members]**

47. Draft and circulate the filing letter using the appropriate letter template, upon concurrence of a filing decision, if applicable (efficacy supplements). At a minimum the filing letter must include the following: **[RPM]**

a. The planned review timeline;

b. Target dates for communication of FDA feedback on proposed labeling, postmarketing requirement (PMR), and postmarketing commitment (PMC) issues;

c. Preliminary plans on whether to hold an AC meeting to discuss the supplement;

d. Any deficiencies identified at the time of the issuance of the filing letter.

Note: if deficiencies are identified in the filing letter, then a Day-74 letter is not required. If deficiencies are identified, but not yet ready to be incorporated into the filing letter, a Day-74 letter is required.

48. Send the filing letter for signature, if applicable. **Note**: if deficiencies are included, circulate to Review Committee Members and supervisors for their review and collate revisions into finalized version. **[RPM, Review Committee Members]**

49. Sign the filing letter and send it to the RPM, if applicable. **[Division Director]**

50. Enter the filing letter issuance date into the appropriate system, upload letter through CBER Connect, and issue the letter to the applicant, if applicable. **[RPM]**

E. Product Testing, Inspections and Lot Release

51. Identify if the changes will impact the Laboratory Quality Product Testing Plan. These may be any type of change. Confer with DBSQC. **Note:** if yes, see section on *Laboratory Quality Product Testing Process*. **[Chair, CMC Reviewer, DBSQC/LIB reviewer, PRB, Stat Reviewer]**

52. Identify if the changes will impact the Lot Release Protocol Template. These may be any type of change. Confer with DBSQC. **Note:** if yes, see section on *Changes to Lot Release Protocol Template Process*. **[Chair, CMC Reviewer, DBSQC/LIB reviewer, PRB, Stat Reviewer]**

53. Identity if in-support testing will be needed. **Note**: if yes, see section on *Testing in Support of the Supplement Process*. **[Chair, RPM, CMC Reviewer, Testing Lab(s), DBSQC and/or LIB]**

54. Determine whether facility inspections are needed. **Note**: if yes, see the *Pre-Approval Inspection Process* section. **[Clinical/OCBQ BIMO Reviewer and DMPQ Reviewer or if a blood establishment DBCD Reviewer]**

55. Confirm the BIMO inspection sites. **[BIMO Reviewer]**

F. Deficiencies Identified/Day 74 Letter (efficacy supplements only)

56. Document in a review memorandum with supervisory concurrence any *potential* issues that should be communicated to the applicant by day 74 of the receipt of the supplement. **[Review Committee Members]**

- **a.** This review memorandum may be a formal memorandum or take the form of an email, so long as the supervisor has been copied. It is up to the discretion of the reviewer and supervisor to determine which documentation method is used.

- **b.** Regardless of method used, the documented review memorandum must be entered into the appropriate regulatory system as a filing memorandum.

57. Draft a Day 74 (Deficiencies Identified) letter that includes all issues identified during the filing review if the deficiencies were not identified in the filing letter. Circulate to the review committee for comments. **[RPM, Review Committee Members, Chair]**

58. Collate and finalize revisions and send to the Division Director for signature. **[RPM]**

59. Issue the Deficiencies Identified letter to the applicant and upload it through CBER Connect. **[RPM]**

G. Review Tasks Continued

60. Schedule the PeRC meeting. **[RPM]**

- **a.** Review the PeRC Scheduling Process document on FDA's PeRC Information Page web page.

61. Issue BIMO inspection assignments to ORA and request completion within 90 days (foreign inspections may take longer). **[OCBQ/BIMO]**

62. Prepare a reviewer report (efficacy supplements only) or review memorandum that documents the reviewer's assessment and identifies any issues with information contained in the submission. See *T 910.09: Reviewer Report*. **[Review Committee Members]**

63. Send the reviewer report/review memorandum to the RPM, Chair, and appropriate supervisor. **[Review Committee Members]**

64. Prepare the internal mid-cycle meeting agenda using *T 910.06*: *Mid-Cycle Meeting Agenda/Summary (efficacy supplements and DMPQ chaired PAS CMC supplements, only).* Distribute the agenda and reviewer reports to meeting attendees at least 2 days prior to the meeting date. **[RPM]**

65. Conduct the mid-cycle meeting ensuring the following are addressed: **[RPM, Chair]**

- **a.** Discuss the progress of the review.

b. Present all substantive issues, major deficiencies, safety concerns and resolution plans.

c. Obtain supervisory feedback.

d. Outstanding IRs or new IRs that the review team plans to send to the applicant, with disciplines identified.

e. Determine post marketing commitments and/or post marketing requirements.

f. Discuss any pending or completed actions for PeRC.

g. Summarize the remaining review schedule for major target dates and actions by review members.

h. Establish a plan to review the label.

i. Updates regarding AC meeting, including the proposed date and plan for the meeting, if applicable.

j. Discuss status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval. Ensure notification of intent to inspect manufacturing facilities has been issued.

Note: The mid-cycle meeting should be conducted face-to-face for all efficacy supplements; it may be conducted by email for manufacturing and labeling supplements.

66. Resolve any scientific issues with the review team and management. **[Chair]**

67. Draft the mid-cycle meeting summary and send it to meeting attendees and appropriate supervisors. **[RPM]**

a. Review, and comment, or concur on the mid-cycle meeting summary. **[Review Committee Members]**

b. Obtain concurrence, finalize draft, and send to Chair for e-signature. **[RPM]**

c. Upload mid-cycle meeting summary through CBER Connect. **[RPM]**

68. Send IRs as needed to facilitate review, referring to the Information Requests (IR) Process section L, below. **[RPM, Review Committee Members]** IR communications should include the four essential components of Four-Part Harmony:

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

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

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

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

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

ii. 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*.

69. Notify the applicant if the product is going to an AC (efficacy supplements only). **[Chair, RPM]**

70. Schedule labeling meeting(s) as needed. Refer to *SOPP 8412: Review of Product Labeling* for additional information. **[RPM]**

71. Convey labeling comments to the applicant and document labeling communications. **[RPM]**

72. Notify CBER's Safety Working Group (SWG) Office Representative of any Title IX PMR/Safety-Related PMC studies needed. Refer to *SOPP 8415: Procedures for Developing Postmarketing Requirements and Commitments* for additional information. **[RPM, Chair]**

73. Coordinate with CBER's SWG executive secretary to schedule a CBER SWG meeting to discuss and obtain concurrence on any proposed Title IX or Safety-Related PMC. **[SWG Office Representative]**

74. Confirm that the PeRC meeting is scheduled, if applicable. **[RPM]**

75. Prepare and submit required PeRC forms in accordance with the PeRC materials table on FDA's PeRC Information Page web page. **[Chair, RPM, Clinical Reviewer]**

76. Present at the PeRC meeting. **[Chair, RPM, Clinical Reviewer, as appropriate]**

77. Draft all proposed PMR(s), safety-related PMC(s) 506(B) PMC(s), and non-506(B) PMC(s). **[Clinical, OBPV/DPV, Product Reviewer(s)]**

[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).

78. Notify the applicant of all proposed PMR(s)/PMC(s) and request feedback or concurrence of study(ies) and agreement on milestone dates. **[Chair, RPM Clinical, OBPV/DPV Reviewer]**

79. Upon applicant agreement of PMR/PMC language, provide final version to review committee members, supervisor(s) and the Office PMR/PMC Coordinator. **[RPM]**

80. If a CE claim is included in the supplement, ensure its review is documented. Refer to *JA 910.20: Procedures for Environmental Assessments and Claims of Categorical Exclusion* for instructions for reviewing and documenting the CE. **[Chairing Office]**

81. If an EA was submitted, ensure it has been reviewed and that review is documented as recommended in *JA 910.20: Procedures for Environmental Assessments and Claims of Categorical Exclusion*. **[Product Office]**

82. Ensure Components Information Table is included in the review memorandum if appropriate. See *SOPP 8401.5: Processing of Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements.* (***Efficacy and CMC supplements***) **[CMC Reviewer]**

H. Review Wrap-up

83. Finalize the Primary Discipline Review Memo(s) and any review addendums, and route to supervisory chain for sign-off. **[Review Committee Members]**

84. Determine decision to either approve or CR the supplement. **[RPM, Chair]**

85. Perform secondary discipline review of any primary discipline reviews and review addendums: **[Supervisors]**

a. If the decision is to concur with the recommendation, a signature on the primary discipline review memorandum is sufficient.

b. If the decision is to non-concur, document the decision and the reasons in a separate review memorandum.

c. Upload the final secondary review memo through CBER Connect and notify the RPM and Chair.

86. Confirm the final discipline review memo and all addendums are in the CER. **[RPM]**

I. Amendment Process

1. Receive, digitally image, process, and notify the appropriate Office through the CER load notification. **[DCC]**

2. Classify the amendment (regular, major, incomplete response to CR, etc.), enter the Short Summary and select the Review Committee Members in the appropriate system. **[RPM]**

3. Confirm that the amendment is properly classified and begin review. **[RPM, Chair and Review Committee Members]**

   a. Major Amendments

      i. Notify the applicant following the procedures in *SOPP 8402: Designation of Amendments as Major*, if the amendment is major. **[RPM]**

      ii. Reschedule previously scheduled meetings to accommodate the PDUFA date extension, as applicable. **[RPM]**

      iii. **Note:** Only one major amendment is allowed per review cycle.

   b. Resubmissions

      i. If the amendment is in response to a CR letter, follow the procedures in *SOPP 8405.1: Procedures for Resubmissions of an Application or Supplement.*

J. Complete Response (CR) Actions

1. Provide review memorandum and CR letter-ready comments, approved by the supervisory chain, to the Chair and RPM. **[Review Committee Members]**

2. Include any compliance issues and/or pending status of inspections in the CR letter. **[RPM, DMPQ Reviewer]**

3. Draft and circulate CR letter for comment. **[RPM]**

4. Collate and finalize revisions to the CR letter and send it to the division director for signature. **[RPM]**

5. Sign the CR letter and return it to the RPM. **[Division Director, RPM]**

6. Notify the applicant of the CR, issue the CR letter, and upload through CBER Connect. **[RPM]**

7. Ensure all documents or communications are entered into the appropriate regulatory system. **[Review Committee Members]**

8. Ensure the product information, including the indication, dosage form, and potency information has been entered into the Product Information screen, if applicable. **[RPM]**

K. Approval Actions

1. Send a compliance check request if applicable, using template *T900.04 – Compliance Check Requests,* 30 days before the projected approval or action due date. **Note**: Refer to *SOPP 8407: Compliance Status Checks* and see *JA 900.10 - Compliance Check Requests* for instructions. **[RPM or DMPQ]**

2. Ensure product dating was determined, if applicable (expiration dates have been established). **[Chair, CMC Reviewer]**

3. Ensure final labeling issues were addressed, if applicable, and final draft labeling has been submitted. Refer to *SOPP 8412: Review of Labeling* for more information. **[Chair, RPM]**

4. If there are lots associated with the submission, refer to the Lot Release Clearance Section **[RPM, DMPQ review committee member]**

5. Ensure the submission details in the STN Special Characteristics field and the indication, dosage form and potency information are correct in the system. **[RPM]**

6. Draft press release if needed and coordinate approval with supervisor. **Note**: warranted for a novel product or indication. Provide CBER press release office in OCOD with the following: **[Chair, Product Office Press Liaison]**

    a. Draft press release or key points, and

    b. Draft labeling

7. Draft and circulate the approval letter to review committee members, ensuring: **[Chair, RPM]**

    a. Lot release instructions are included if applicable;

    b. PMRs/PMCs are addressed following the format outlined in the approval letter template, and

    c. PREA is addressed, as appropriate.

8. Send the approval letter for signature to all appropriate review office's branch chiefs and division directors for concurrence. **[Chair, RPM]** Note: a link to the electronic Action Package (eAP) may be included for Office Director's reference and review during the sign-off process.

9. Sign the approval letter. **[Division Director]**

10. Upload the approval letter into the appropriate regulatory system**. [RPM]**

11. Communicate approval to applicant. **[Chair, RPM]**

12. Perform a final check to ensure that all documents and communications were entered into the appropriate regulatory system. **[Review Committee Members]**

13. Perform a quality control review of the CBER generated documents related to the application, ensuring that all documents are in the CER, dates are correct, and documents are properly signed; the eAP can be used as a resource. **[RPM]**

14. Ensure the action package for posting documents are sent to the Office of Communications, Outreach and Development (OCOD) per *JA 910.07 – Posting Procedures for BLA/NDA Supplements*, on approval date. **[RPM]**

15. Complete the Review Completion Process in the appropriate system. This changes the status of the product to "Approved". **[RPM]**

16. Enter PMRs and PMCs into CBER's regulatory system. **[Office PMR/PMC Regulatory Coordinator]**

17. Complete the electronic Filing Action Package (eFAP) for submission to DCC, refer to *DCC Procedure Guide #23: Procedure for Filing Final Action Packages Containing Electronic FDA Communications for Marketing Applications*. **[RPM]**

18. Return any documents (submission file) that need information corrected in the regulatory system. **[DCC]**

19. Make any necessary corrections in the regulatory system before the 30-day system lockdown. **[Review Committee Members]**

L. Information Request (IR) Process

1. Draft IRs to the applicant, as needed, to include the four essential components of Four-Part Harmony and ensure the requests are directed through the RPM and Chair. **[Review Committee Members]**

2. Issue IR(s) to the applicant as needed to facilitate the review. **[RPM]**

3. Enter the IR(s) as communications into the appropriate system and upload through CBER Connect. **[RPM]**

M. Pre-Approval Inspection Process

1. Determine if a pre-approval inspection (PAI) is necessary for approval; refer to *SOPP 8410: Determining when Pre-License/Pre-Approval Inspections are Necessary* for more information. **[DMPQ or DBCD CMC Reviewer]**

2. Request ORA to perform any required PAIs for NDA, if applicable; work with the Division of Inspections and Surveillance to issue a directed inspection assignment(s) as necessary **[DMPQ or DBCD CMC Reviewer through DIS]**

a. Except for ORA directed inspections of blood establishments sent through DIS, plan and conduct blood establishment PAIs. **[DBCD CMC Reviewer]**

3. Review 483 responses as they arrive. If the response(s) is complete and adequate, issue memo(s) with supervisory approval to close out inspection. **[Lead Inspector, CMC Inspector(s)]**

4. Send appropriate sections of the EIR to the respective inspection lead(s), if applicable. **Note**: EIR(s) must be completed regardless of final action. **[Lead Inspector, CMC Inspector(s)]**

5. Enter the final EIR(s) in the appropriate system and upload through CBER Connect. **[Lead Inspector]**

6. Prepare endorsement memo **[Lead DMPQ Inspector or for blood establishment PAIs conducted by DBCD, by DCM]**

7. Verify Lead Inspector closes out inspection(s) and uploads endorsement(s) through CBER Connect, when possible. **Note**: If the inspection cannot be closed prior to approval, then the final action must result in a CR. **[DMPQ RPM or DBCD Reviewer]**

8. Send Inspection Tab, including the EIR with exhibits and attachments, and any other paper communications and amendments, to DCC. **[DMPQ RPM or DBCD Reviewer]**

9. Enter date(s) of FMD-145 letters into the appropriate system. **[OCBQ/DIS]**

N. Laboratory Quality Product Testing Plan Process

1. Draft and circulate the Laboratory Quality Product Testing Plan (TP) to Product Office and DBSQC CMC Reviewers for review. **[DBSQC Regulatory Coordinator (RC) or LIB Rep]**

2. Review and address comments and revise the TP as needed. Route the draft Laboratory Quality Product Testing Plan to DBSQQC management (division director, appropriate lab chief, and Quality Assurance) for review and approval in the Integrated Quality System (IQS). **[DBSQC RC]**

3. Submit final Laboratory Quality Product Testing Plan for signature to DBSQC Director, Product Office Directors (based on STN), Office Directors (based on STN), DMPQ Director and Center Lab Quality Director. **Note**: DBSQC or LIB Representative enters final Laboratory Quality Product Testing Plan information into the appropriate system. **[DBSQC RC or LIB Rep]**

O. Changes to Lot Release Protocol Template Process

1. Determine, after collaboration, the post-licensure manufacturer's Lot Release Protocol requirements for products subject to lot release or surveillance. **[Chair, CMC Reviewer/Product Lead, DBSQC or LIB, PRB, Statistical Reviewer]**

2. Verify Post-Licensure Lot Release Protocol reviewer(s) and notify PRB of any change in reviewer(s). **[DBSQC RC or LIB Rep and DMPQ/PRB Chief]**

3. Revise Data Collection Plan(s) for the Lot Release Protocols. **[Lot Release Protocol Reviewers]**

4. Enter Data Collection Plan(s) into the appropriate system and upload through CBER Connect. **[Lot Release Protocol Reviewers]**

P. Testing in Support of the Supplement Process

1. When releasable lots will be used for testing in support:

   a. Request that the applicant send samples to the Sample Custodian. **[Chair]**

   b. Email completed PRB Form-201 to request samples. **Note**: blank PRB Form-201 is provided by the PRB Branch once samples arrive. **[Chair]**

   c. Conduct testing. Prepare Testing in Support Results Memo. **[Testing Labs]**

   d. Enter and upload the memo into the appropriate regulatory system. **[Testing Labs]**

   e. Enter testing outcome in LRS. **[Testing Labs]**

   f. Review Testing in Support Results Memo and comment in CMC review memo as needed. **[CMC Reviewer]**

2. When samples do not represent releasable lots:

   a. Request that the applicant send samples to the testing labs. **[Chair]**

   b. Conduct testing. Prepare Testing in Support Results Memo. **[Testing Labs]**

   c. Enter and upload the memo into the appropriate regulatory system. **[Testing Labs]**

   d. Review Testing in Support Results Memo and comment in CMC review memo as needed. **[CMC Reviewer]**

Q. Lot Release Clearance Process (for products subject to lot release)

1. Obtain Lot Release Clearance by emailing the CBER Outlook account for lot release clearance. **[RPM]**

2. Provide DMPQ/PRB and DIS/PSB with copies of the Approval letter via email to the CBER Outlook lot release account, so that PRB may complete the lot release process and PRB may share the Approval Letter with ORA. **[RPM]**

3. Provide notification of release to the applicant for any lots, as appropriate. **[OCBQ/DMPQ/PRB Reviewer]**

VIII. Appendix

N/A

IX. References

A. References below are CBER Internal:

1. Document Control Center Procedures

   a. DCC Procedure Guide #11: Procedure for Filing Pre-License/Pre-Approval Inspection Material

2. Checklists

   a. C 905.01: RPM Filing Review Checklist for BLA, NDA, and Efficacy Supplements

   b. C 910.04: PDUFA Checklist for Original BLAs and Supplements

3. Regulatory Job Aids

   a. JA 860.03: Instructions for Completing the PMR/PMC Annual Report Review Form (PARRF)

   b. JA 910.06: Completing a Filing Review

   c. JA 910.02: Proprietary Name Review Processing

   d. JA 910.07: Posting Procedures for BLA/NDA Supplements

   e. JA 910.08: Lockdown of Applicant Submissions and CBER Correspondence for Marketing Submissions

   f. JA 900.10: Compliance Check Requests

   g. JA 910.14: Labeling Review – Pregnancy, Lactation, and Females and Males of Reproductive Potential

   h. JA 900.18: Study Data Validation Process

i. JA 910.20: Procedures for Environmental Assessments and Claims of Categorical Exclusion

j. JA 910.22: Procedures for Upper Center Management Leadership Briefing Before Issuing a Refuse-to-File (RTF) Letter

4. Regulatory Templates

a. T 900.04: Compliance Check Request

b. T 910.09: Reviewer Report

c. T 910.15: First Committee Meeting Agenda/Summary

d. T 910.16: Filing Meeting Agenda/Summary

e. T 910.06: Mid-Cycle Meeting Agenda/Summary

5. Review Template Letters

6. PeRC Information Page

7. Standard Operating Policies and Procedures (SOPPs)

a. SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements

B. References below can be found on the Internet.

1. Statutes and Regulations

a. CFR – Code of Federal Regulations Title 21

b. Federal Food, Drug, and Cosmetic Act (FD&C Act)

c. Food and Drug Administration Amendments Act (FDAAA) of 2007

d. User Fee Acts

i. Biosimilar User Fee Act (BsUFA)

ii. Prescription Drug User Fee Act (PDUFA)

2. Guidance Documents

a. Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees

b. Guidance for Industry: Providing Regulatory Submissions in Electronic Format: Certain Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications

c. Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans

d. Draft Guidance for Industry: Pediatric Drug Development: Complying with the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceutics for Children Act

e. Guidance for Industry: Chemistry, Manufacturing and Controls Changes to an Approved Application: Certain Biological Products

f. Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture

3. Standard Operating Policy and Procedures

a. SOPP 8119: Use of Email for Regulatory Communications

b. SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Applications

c. SOPP 8402: Designation of Amendments as Major

d. SOPP 8404: Refusal to File Procedures

e. SOPP 8405.1: Procedures for Resubmissions of an Application or Supplement

f. SOPP 8407: Compliance Status Checks

g. SOPP 8410: Determining When Pre-License/Pre-Approval Inspections are Necessary

h. SOPP 8412: Review of Product Labeling

i. SOPP 8415: Procedures for Developing Post-marketing Requirements and Commitments

4. FDA Forms

a. Form 356h: Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use

b. Form 3674: Certification of Compliance, under 42 U.S.C. §282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. §282(j))

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Valencia/ Monser/ Laughner	Katie Rivers, Chief, RABOB/DROP/ ORO	February 8, 2024	10	Added additional reviewer types, updates for PDUFA VII changes related to discussion on inspection status and PMR/PMCs; harmonized applicable procedures with SOPP 8401.
Martha Monser	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	September 22, 2023	9	Updated: 1) include RTF briefing in meetings for efficacy supplements, and 2) efficacy supplement definition. Added to policy 1) that if a supplement is RTF'd and not FOP, no additional submissions can be added to the file, and 2) DI are usually communicated in FL, not a Day 74 letter.
Lynch/Monser/ Ryan	Darlene Martin, MS, PMP ORO/DROP Director (acting)	September 28, 2022	8	Updated for PDUFA VII
Martha Monser	Christopher Joneckis, PhD	December 17, 2021	7	Updated procedures for study data validation in accordance with JA 900.18, updated approval actions section to be consistent with current practices.
Martha Monser	Darlene Martin, MS, PMP	March 7, 2021	6	Update to add JA 910.20
Martha Monser	N/A	December 11, 2020	5	Technical update for retirement of EDR and replacement with CBER Connect /CER.
Carla Vincent, Martha Monser	Christopher Joneckis, PhD	August 26, 2019	4	Major revision to reflect policy and procedural changes.

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Leonard Wilson, RMCC	Robert Yetter, PhD	2/11/2003	3	Changes to accommodate incorporation of SOPP 8401.3, Filing Action: Communication Options
Leonard Wilson, RMCC	Robert Yetter, PhD	10/1/2002	2	Changes to accommodate PDUFA III and other updates
S. Risso, RMCC	Robert Yetter, PhD	7/26/2002	1	Original