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 of 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 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;
   - Incorporate other information based on at least one adequate and well-controlled clinical study.

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 *Draft 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 356h form 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. 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.

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

H. 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).
I. 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.

J. 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, unless a serious safety issue is involved. 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.

K. 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.

L. 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.

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

1. Chemistry, Manufacturing and Control (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 contain-closure integrity.

N. 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.

O. 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).

P. 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).

Q. Filing Meeting:

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 database/system and imported into CBER's Electronic Document Room (EDR).

5. The filing meeting summary must also be entered into the appropriate database/system and imported to the EDR by day 60.
R. Unsolicited amendments are discouraged; however, in some cases (e.g., new adverse reaction, safety information, manufacturing information, etc.) such amendments may be necessary.

S. 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).

T. 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.

U. 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.

V. All communications, including telephone calls and other informal communications, are to be continuously entered into the appropriate regulatory database in real time; all documents should be uploaded to CBER’s EDR. All letters issued by CBER must use the most recent approved template.

W. Defined dates used on CBER correspondence and entered into CBER databases/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).

X. All CBER correspondence should be entered into the appropriate database/system and imported to the EDR 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 CBER’s EDR, 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 databases 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 database/system and uploads to CBER’s EDR. 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 Document Room (EDR). Notify the appropriate Office through the EDR 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 database/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 database/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. (See Reference section for link to the guidance.) [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 database/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 database/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 database/system, as applicable. [RPM]
8. Ensure all relevant information pertaining to the applicant, regulatory contact and manufacturing facilities reflected in the appropriate database/system and on form 356h are correct. [RPM]

9. If Study Data Tabulation Model (SDTM), Analysis Data Model (ADaM) data, Standard for Exchange of Nonclinical Data (SEND) or CTD datasets - Module 5 are present, notify CBER’s Clinical Data Interchange Standards Consortium (CDISC) representative and request that a CDISC format validation be performed. **Efficacy supplements only** [RPM] Note: SDTM data would be labeled: STUDYID, DOMAIN, USUBJID, --SEQ (-- is AE, DS, or EX). Refer to JA 900.18: Study Data Validation for more information

   a. If there are validation errors, the CDISC reviewer will contact the RPM.

   b. If revisions/corrections are needed, the RPM will send an Information Request (IR) to the applicant.

   c. Ensure that the “CDISC” STN Characteristic is entered into the Submission Information screen.

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 [RPM]

      ii. 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. Statistical Reviewer of Clinical Data
   l. Statistical Reviewer of Non-clinical Data
   m. Postmarketing Safety Epidemiological Reviewer
   n. OCBQ/APLB Promotional Reviewer
   o. OCBQ/APLB PNR Reviewer
   p. OCBQ/BIMO Reviewer
   q. OCBQ/DBSQC or OVRR/DBPAP/LIB Reviewer
   r. Consult Reviewer(s)
   s. OCBQ/DMPQ/Lead Inspector
   t. CMC Inspector
   u. 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 database. [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 your 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. Issue an STN Acknowledgment letter to the applicant and upload to the EDR. [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.

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

   • First committee meeting
   • Filing decision
   • Mid-cycle meeting
   • Labeling meetings
Other meetings as necessary

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

C. First Committee Meeting

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

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

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

26. Draft and distribute agenda for the First Committee Meeting. (Use template: T 910.15: First Committee Meeting Agenda/Summary) [RPM]

27. 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. (see 25.a), 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]

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

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

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

31. Sign the first committee meeting summary and send to the RPM. [Chair]

32. Enter meeting summary/minutes into the appropriate database/system and upload to 
   the EDR. [RPM]

D. Filing Decision/ Meeting

33. 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]

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

35. 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.

36. 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. Enter all documentation in the appropriate database/system and import to the EDR.

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

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

38. Upload the filing checklist or review memo to the EDR. Note: enter the name of the specific review discipline in the Summary Text. [Review Committee Members]

39. 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]

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

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

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

43. Enter the filing meeting date or filing memorandum date into the appropriate database/system. [RPM]

44. Upload the Filing Meeting Summary to the EDR (efficacy supplements only). [RPM]

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

47. 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]

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

49. Enter the filing letter issuance date into the appropriate database/system, upload letter to the EDR, and issue the letter to the applicant, if applicable. [RPM]

E. Product Testing, Inspections and Lot Release

50. 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]

51. 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]

52. 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]

53. 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]
54. Confirm the BIMO inspection sites. [BIMO Reviewer]

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

55. 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 database/system as a filing memorandum.

56. 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]

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

58. Issue the Deficiencies Identified letter to the applicant and upload to the EDR. [RPM]

G. Review Tasks Continued

59. Schedule the PeRC meeting. [RPM]


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

61. 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]

62. Send the reviewer report/review memorandum to the RPM, Chair and your supervisor. [Review Committee Members]

63. 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]

64. 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 plans to resolve them
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.

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.

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

66. Draft the mid-cycle meeting summary and send 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 to the EDR. [RPM]

67. Send IRs as needed to facilitate review. Refer to the Information Requests Process section. [RPM, Review Committee Members] 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.

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

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

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

71. Notify CBER’s Safety Working Group (SWG) Office Representative of any PMR/PMC studies needed. Refer to SOPP 8415: Procedures for Developing Postmarketing Requirements and Commitments for additional information. [RPM, Chair]
72. Coordinate with CBER’s SWG executive secretary to schedule internal meetings, including a CBER SWG meeting and meetings with the applicant if there are any Title IX PMR(s) and/or clinical PMC(s) that will be required. [SWG Office Representative]

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

74. Prepare and submit required PeRC forms in accordance with the PeRC materials table on FDA’s PeRC Information Page website (See link to PeRC information under References). [Chair, Clinical Reviewer]

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

76. Draft all proposed PMR(s), and clinical and non-clinical PMC(s). [Chair, RPM Clinical, OBE DE Reviewer]
   a. Send proposed PMR(s)/PMC(s) to SWG Office Representative.
   b. Present proposed PMR(s)/PMC(s) at the SWG meeting, if applicable.
   c. Make revisions/schedule additional meetings as necessary.

77. Send letter-ready PMR(s)/PMC(s) to the SWG executive secretary for review and comment. [SWG Office Representative]

78. Notify the applicant of all proposed PMR(s)/PMC(s) and request feedback or concurrence. [Chair, RPM Clinical, OBE DE Reviewer]

79. Upon applicant agreement of PMR/PMC language, provide final version to review committee members, Supervisor and Office PMR/PMC Coordinator. [RPM]

80. Ensure Categorical Exclusion (CE) claim is documented in the discipline review memo, if applicable. [Chairing Office]

81. Ensure Environmental Assessment (EA) has been reviewed and that review is documented, if applicable. [Product Office RPM]

82. Ensure Components Information Table is included in 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 to the EDR and notify the RPM and Chair.

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

I. Amendment Process

1. Receive, digitally image, process, and notify the appropriate Office through the EDR 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 database/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 to the division director for signature. [RPM]

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

6. Notify the applicant of the CR, issue the CR letter, and upload to the EDR. [RPM]

7. Ensure all documents or communications are entered into the appropriate database/system and uploaded to the EDR. [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. Ensure the submission details in the STN Special Characteristics field and the indication, dosage form and potency information are correct in the database/system. [RPM]

5. 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.

6. Route approval letter for signature to all appropriate review office’s branch chiefs and division directors for concurrence. [Chair, RPM]

7. Sign the approval letter. [Division Director]
8. Upload the approval letter to the EDR. [RPM]

9. Communicate approval to applicant. [Chair, RPM]

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

11. Perform final check to ensure all documents and communications were uploaded to the EDR and all other relevant information are entered into the appropriate database/system. **Note**: RMS-BLA and EDR lockdown 30 days post approval. [Review Committee Members]

12. 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]

13. Draft press release if needed and coordinate approval with supervisor. **Note**: warranted for a novel product or indication. **Efficacy supplements only** Provide CBER press release office in OCOD with the following: [Chair]
   a. Draft press release or key points, and
   b. Draft labeling

14. Complete the electronic Filing Action Package (eFAP) for submission to DCC. [RPM]

15. Return any documents (submission file) that need information corrected in RMS-BLA. [DCC]

16. Make any necessary corrections in RMS-BLA before the 30-day system lockdown. [Review Committee Members]

17. Complete the Review Completion Process in the appropriate database/system. This changes the status of the product to “Approved”. [RPM]

L. Information Request (IR) Process

1. Draft IRs to the applicant, as needed, ensuring 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 database/system and upload to the EDR. [RPM]

M. Pre-Approval Inspection Process
1. Determine if a pre-approval inspection (PAI) is necessary for approval. Please 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 database/system and upload to the EDR. [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) to the EDR, 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 database/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, 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 database/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 database/system and upload to the EDR. [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 memo into the appropriate database/system and upload to the EDR. [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 memo into the appropriate database/system and upload to the EDR. [Testing Labs]
   d. Review Testing in Support Results Memo and comment in CMC review memo as needed. [CMC Reviewer]

**Q. Lot Release Clearance Process**

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. C910.04: PDUFA Checklist for Original BLAs and Efficacy 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

4. Regulatory Templates
a. T900.04: 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. T910.06: 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
   
   
   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


   d. Draft Guidance - How to Comply with the Pediatric Research Equity Act
e. Draft Guidance for Industry: Chemistry, Manufacturing and Controls Changes to an Approved Application: Certain Biological Products

f. 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 Communication

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


X. History

<table>
<thead>
<tr>
<th>Written/Revised</th>
<th>Approved By</th>
<th>Approval Date</th>
<th>Version Number</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carla Vincent, Martha Monser</td>
<td>Christopher Joneckis, PhD</td>
<td></td>
<td>4</td>
<td>Major revision to reflect policy and procedural changes.</td>
</tr>
<tr>
<td>Written/Revised</td>
<td>Approved By</td>
<td>Approval Date</td>
<td>Version Number</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Leonard Wilson, RMCC</td>
<td>Robert Yetter, PhD</td>
<td>2/11/2003</td>
<td>3</td>
<td>Changes to accommodate incorporation of SOPP 8401.3, Filing Action: Communication Options</td>
</tr>
<tr>
<td>Leonard Wilson, RMCC</td>
<td>Robert Yetter, PhD</td>
<td>10/1/2002</td>
<td>2</td>
<td>Changes to accommodate PDUFA III and other updates</td>
</tr>
<tr>
<td>S. Risso, RMCC</td>
<td>Robert Yetter, PhD</td>
<td>7/26/2002</td>
<td>1</td>
<td>Original</td>
</tr>
</tbody>
</table>