

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

Version: 8

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I. Purpose

- A.** This Standard Operating Policy and Procedure (SOPP) serves as a guide to Center for Biologics Evaluation and Research (CBER) staff on the administrative processing of Biologics License Applications (BLA) and New Drug Applications (NDA).

II. Scope

- A.** This SOPP applies to original BLAs and NDAs processed by CBER including those subject to the Biosimilar User Fee Act (BsUFA) and the Prescription Drug User Fee Act (PDUFA).
- B.** This procedure does not apply to:
 - 1.** BLAs subject to the Medical Device User Fee Act (MDUFA)
 - 2.** Abbreviated New Drug Applications subject to the Generic Drug User Fee Act (GDUFA).
 - 3.** Annual reports

III. Background

- A.** The Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce. A BLA is submitted by an applicant (manufacturer) and must contain data derived from non-clinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency (21 CFR Part 601.2).
- B.** The New Drug Application (NDA) is the vehicle through which applicants formally propose that a new drug be approved for sale and marketing in the United States (Federal Food, Drug and Cosmetic (FD&C) Act Section 505(b)).
- C.** The Patient Protection and Affordable Care Act amended the Public Health Service (PHS) Act to create an abbreviated licensure pathway for biological products that are demonstrated to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product. The Biosimilar User Fee Act (BsUFA) authorized FDA to assess and collect fees for biosimilar products.
- D.** The Prescription Drug User Fee Act (PDUFA) authorized FDA to collect user fees from manufacturers of certain human drug and biological products.

- 1.** PDUFA V established a review model, known as the Program, for original BLAs and new molecular entity (NME) NDAs. The goal of the Program is improving the efficiency and effectiveness of the first cycle review process and decreasing the number of review cycles necessary for approval through improved communication and greater transparency.
 - 2.** Products subject to PDUFA user fees include most human drugs and biological drug products. Products exempted from PDUFA include the following:
 - a.** Whole blood or a blood component for transfusion;
 - b.** Bovine blood product for topical application licensed before September 1, 1992;
 - c.** Allergenic extracts;
 - d.** Cord blood and peripheral blood stem cells separated from whole blood by physical or mechanical means for transfusion;
 - e.** An *in vitro* diagnostic biologic product licensed under section 351 of the PHS Act. (These BLAs are subject to MDUFA.);
 - f.** A biological product licensed for further manufacturing use only.
- E.** CBER developed the Managed Review Process (MRP) with the goal of providing a process to most effectively and efficiently review all user fee and non-user fee license applications and supplements. This process begins during the investigational phase which builds the foundation of information necessary to demonstrate safety, efficacy and capability of consistent manufacture of a drug or biological drug product and continues through the postmarketing phase.
- 1.** The MRP incorporates the information contained in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*, including quality, efficiency, clarity, transparency, and consistency during the review process.
 - 2.** CBER's MRP consists of all CBER regulatory SOPPs, checklists, job aids, references, and templates, including letter and review templates that help CBER's review community carry out their review responsibilities.
- F.** Complementary to the MRP during the review and decision making process are Advisory Committees (ACs). They provide independent advice and recommendations to the FDA on scientific and technical matters related to the development and evaluation of products regulated by the Agency. FDA requests advice from ACs on a variety of matters, including various aspects of clinical investigations and applications for marketing approval of drug products. Advisory Committee members are scientific experts such as physician-researchers and statisticians, as well as representatives of the public, including patients. Although the ACs provide recommendations to the Agency, final decisions are made by FDA.

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 from the applicant that the Agency has not requested.
- 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 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. Establishment Inspection Report (EIR)** – the report issued at the conclusion of an establishment inspection that summarizes the inspectional findings.
- E. Expedited Review** – FDA’s review of a human drug application that has received priority review designation where the Review Team (Committee) plans to act at least 1 month before the PDUFA goal date provided that no significant application deficiencies prevent an early action. (PDUFA VI goals letter)
- F. 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.
- G. 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 review.
- H. Late-Cycle meeting** – a meeting held for applications subject to the PDUFA Program with the CBER Review Committee, CBER senior management, and the Applicant to discuss the status of the review of the application late in the review cycle. **Note:** This meeting is not intended to discuss the pending regulatory decision on the application.
- I. 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.
- J. Mid-Cycle Communication** – a phone call to the Applicant that generally happens within two weeks following the internal Mid-Cycle review meeting to provide the Applicant with an update on the status of the review of their submission. **Note:** applies to submissions subject to the PDUFA/BsUFA Programs only.
- K. Primary Discipline Review** – a written review containing a reviewer’s assessment and recommendations of all assigned areas of the original submission.

- L. Priority Review** – a reduced review schedule compared to a standard review schedule to potentially allow the product to reach the market faster.
- M. 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.
- N. Standard Review** – all non-priority applications are considered standard applications.
- O. Substantive Review Issues:** Issues identified to date that may preclude approval if not resolved.
- P. Review Memorandum Addendum** – information appended to a previously finalized review memorandum. **Note:** This addendum may include a written review of any amendments that have been accepted for review by CBER since the primary discipline review was completed and documented, any AC recommendations, and/or results or actions stemming from issuance of an Establishment Inspection Report (EIR).
- Q. Summary Basis of Regulatory Action (SBRA)** – a summary of all relevant and pertinent information from the review of a BLA or NDA. **Note:** The SBRA documents conclusions from all review disciplines (clinical/statistical, CMC, pharmacology/toxicology, etc.) about the product, notes any critical issues and disagreements with the Applicant and within the FDA Review Committee and how they were resolved, provides recommendations for action and an explanation of any non-concurrence with review conclusions, and provides a detailed discussion of areas in which there were notable issues, unusual aspects or problems with the data or analysis, novel features of design or conduct of studies.

V. Policy

- A.** All new marketing applications for products subject to licensure under the Public Health Service (PHS) Act are handled as BLAs or supplements to BLAs. The procedures in this SOPP are not inclusive of all detailed procedures used to process applications. This SOPP is to be used with other related SOPPs, such as *SOPP 8412: Review of Product Labeling* and others listed in the references section that describes administrative handling and review of license applications. New Drug Applications (NDA) are managed in the same manner as BLAs where appropriate. Differences in NDA handling are described in the procedure section of this SOPP as needed.
- B.** Requirements for electronic submissions
 - 1.** Under Section 745A(a) of the FD&C Act, sponsors/applicants will be 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).
 - 2.** Submissions that are not submitted electronically and electronic submissions that are not in a format that FDA can process, review, and archive will not be filed or received, 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*, under References, for complete eCTD requirements and exceptions.
- C.** A signed Form FDA 356h should be submitted with all BLA/NDA-related applications and correspondences to CBER. This information will aid in routing the application to the appropriate division for processing. The person who signs an FDA application form (e.g., 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. Accordingly, the signatory of the original application, 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, i.e., originals and amendments. The Applicant is to determine the relevance of the application for compliance with Title VIII of the Food and Drug Administration Amendments Act (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.** Applications filed over protest after a refuse to file decision are not eligible for parameters of the PDUFA Program. The original submission will be subject to the review goals per the current PDUFA goals letter; resubmission goals do not apply. Refer to *SOPP 8404.1: Procedures for Filing an Application when the Applicant Protests a Refusal to File Action (File Over Protest)* for additional information.
- F.** For products covered by user fees, the performance goals established in the most current user fee goals letter will be met.
- G.** Applications for non-user fee products will not be subject to all the procedures of the PDUFA/BsUFA Programs, but instead will be subject to CBER's Managed Review Process. Differences in handling submissions not subject to the PDUFA/BsUFA Programs are described in the Procedures section as needed.
- H.** Review assessment and its documentation starts when the application is received and progresses throughout the review time line, such that the primary discipline review must be nearly complete, if not complete, by the target date in time for the Mid-Cycle meeting.
- I.** Under normal circumstances product lot(s) should be available for distribution at the time of approval of most BLAs. Exceptions will be made on a case by case basis. Please refer to *SOPP 8408.1: Development of Laboratory Quality Product Testing Plans and Release of Lots as Part of the BLA Approval Process* for additional information.
- J.** CBER staff will not discuss the pending regulatory status for 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.

- K.** The original application submission is expected to be complete per 21 CFR 601.2 and 21 CFR 314.
- 1.** For products subject to the PDUFA/BsUFA Programs, the CBER Review Committee Members and the Applicant may agree at the pre-submission meeting on minor application components that are allowed to be submitted not later than 30 calendar days after receipt of the original submission of the application.
 - 2.** For products subject to the PDUFA/BsUFA Programs, the only components allowed to be submitted more than 30 calendar days after the original application include stability and clinical safety updates. Dates when these are to be provided should be discussed at the pre-submission meeting.
 - 3.** Incomplete submission of an application, including failure to provide agreed upon information within 30 days of receipt of the application, will be subject to a refuse to file decision. Please refer to *SOPP 8404: Refusal to File Procedures for Biologic License Applications, New Drug Applications and Efficacy Supplements* for additional information.

L. Review Timeline:

- 1.** For products subject to the PDUFA/BsUFA Programs, the review timeline begins upon acceptance of the original application submission for filing, no later than 60 calendar days from the date that CBER receives the application.
- 2.** For products subject to PDUFA but not subject to the PDUFA Program, the review timeline begins upon CBER receipt of the application.
- 3.** For non-user fee applications, the review timeline begins upon CBER receipt of the application.
- 4.** For products subject to PDUFA: each application will be evaluated on a case-by-case basis to determine if the review timeline will be an expedited, priority or standard review timeline.
 - a.** Products are eligible for priority review if they provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening disease.
 - b.** If the Review Committee determines, after the applicant is notified in the Filing Letter, that an expedited review is no longer appropriate, the timeline will default to priority. The decision for the change in review timelines should be communicated to the applicant within 3 business days of making the decision.
- 5.** For products subject to the PDUFA/BsUFA Programs: timeline Extensions:

- a. If, during FDA's review of an original application, 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.
- b. The submission of a Major Amendment at any time during the review cycle may extend the goal date by 3 months.
- c. Note: there may be only extension during the review cycle.

M. Filing Meeting:

- 1. Filing meetings are expected to occur. Filing meetings for non-user fee products, however, occur as needed when the application is incomplete or other issues are identified by the Review Committee Members.
- 2. Prior to the Filing Meeting each reviewer is expected to document in the appropriate discipline specific Filing Review Checklist or a review memorandum any potential issues with the application that could result in a refuse to file decision or be included in the Deficiencies Identified (Day-74) letter.

N. Review of unsolicited amendments and responses to a Deficiencies Identified (Day-74) letter communication of deficiencies will be handled in accordance with the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*.

O. Mid-Cycle Meeting:

- 1. 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.
- 2. At the Mid-Cycle Meeting each reviewer is expected to discuss key findings documented in the primary discipline review memorandum. A Reviewer Report that summarizes substantive issues copied from the primary review memorandum and a proposed plan to address these issues must be provided by email to the RPM in advance of the meeting.
- 3. For non-user fee products, formal Mid-Cycle Meetings are encouraged and will be conducted on an as-needed basis.
- 4. For products subject to the PDUFA/BsUFA programs, the Regulatory Project Manager (RPM) and the Review Committee Chair will have a Mid-Cycle Communication telecon with the Applicant within two weeks following the Mid-Cycle Meeting to provide an update on the status of the review. Review Committee Members may attend as appropriate for discussion of issues regarding their review discipline.

P. Late-Cycle Meeting for submissions that qualify under the PDUFA/BsUFA Programs:

- 1. The purpose of the Late-Cycle Meeting is to:**
 - a. Discuss the progress of the review**
 - b. Identify and present substantive issues and plans to address those issues**
 - c. Discuss the remainder of the review including possible dates for further deliverables and interactions**
- 2. CBER staff will not:**
 - a. Discuss the pending final regulatory action to the Applicant**
 - b. Make a determination or convey whether a proposal from the Applicant would address a specific issue**
 - c. Make a determination or convey whether a proposal from the Applicant (once received) will be reviewed in the current review cycle.**
- 3. The following must be provided to the RPM prior to the Late-Cycle Meeting:**
 - a. Each discipline reviewer will update the Reviewer Report from the Mid-Cycle Meeting identifying substantive issues to date.**
 - b. The Chair will draft the Late-Cycle Review Committee Memorandum**
- 4. The Office Director and/or Deputy Office Director, Review Committee Members, and team leaders or supervisors from disciplines with substantive issues must be present at the Late-Cycle Meeting. The meeting must be rescheduled if the Office Director or Deputy Office Director cannot attend.**
- 5. Will generally be face-to-face meetings; however, the meeting may be held by teleconference if FDA and the Applicant agree.**
- 6. The Late-Cycle meeting materials will be sent to the Applicant no later than 10 calendar days (or 2 calendar days for an expedited review) prior to the LCM.**

Q. Advisory Committee (AC) meetings:

- 1. For PDUFA products: Should occur no later than two months (standard review) and no later than six weeks (priority review) prior to the user fee goal date.**
- 2. For BsUFA products: should occur no later than 3 months prior to the user fee goal date.**
- 3. The Agency briefing materials will be sent to the Applicant not less than 20 calendar days before the meeting.**

4. Final questions for the AC should be sent to the Applicant and the AC at least two calendar days in advance of the AC meeting.
 5. If the AC is scheduled earlier than when the Late-Cycle Meeting occurs (due to AC scheduling outside the Review Committee's control), only the background materials for the AC meeting will be sent to the Applicant.
- R.** It is critical that the Review Committee Members keep management, including Office and Center senior management, up-to-date with any significant review issues. Additionally, all communications, including telephone calls and other informal communications are to be continuously entered into all appropriate regulatory databases/systems in real time; all documents should be uploaded to CBER's Electronic Document Room (EDR). All letters issued by CBER must use the most recent approved template found on CBER's Review Letter Templates Intranet Web page.
- S.** Defined dates used on CBER correspondence and entered into CBER databases/systems are described in regulatory job aid *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).
- T.** An internal post action meeting may be held with all members of the Review Committee within 45 days of ending the first review cycle (i.e., issuing the first CR or approval) to discuss the Review Committee dynamics, interactions with the applicant, basis of decisions, what worked well, and what didn't work well during the review cycle. The goal is to identify improvements that can be made within Review Committee dynamics and Center or Office procedures. A summary of the meeting including specific recommended changes should be recorded and communicated to the Associate Director for Review Management (ADRM), who will disseminate as appropriate to other CBER staff.
- U.** All CBER correspondence should be entered in the appropriate regulatory database/system and imported into CBER's EDR prior to the final action (e.g., approval, withdrawn, refuse to file). After the final action is taken, applicant amendments will be allowed to the submission for 14 calendar days. Changes to CBER communications/documents will be allowed for 30 calendar days. After these timeframes, a lockdown will be initiated and no additional or revised documents will be added to the submission without approval. Refer to regulatory job aid *JA 910.08: Lockdown of Applicant Submissions and CBER Correspondence for Marketing Submissions* posted on CBER's Intranet 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 sections of the application have been assigned for review, drafting of the SBRA, bringing scientific issues to the attention of management and facilitating resolution and consensus. The Chair works closely with the RPM in executing these duties. (Note: The CDTL as referred to in the PDUFA Program is considered the chair within CBER.)

- B. Office Director, Deputy Office 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 Electronic Document Room (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, 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.
- E. Review Committee Members** – each member performs a review of all assigned areas of submissions, 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 procedure 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 non-user fee products
- 2.** Application reviews are completed using the following process. Each individual process is detailed in the following sections of this SOPP.
- 3.** Review assessment and its documentation starts when the application is received and progresses throughout the review time line, such that the primary discipline review must be nearly complete, if not complete, by the target date in time for the Mid-Cycle Meeting.
- 4.** Refer to *C 910.04: PDUFA Checklist for Original BLAs and Efficacy Supplements* for additional information.

5. Refer to *R 910.04: Expedited Review Information* for additional information on expedited reviews.
6. Refer to *R 910.05: Formal Communication Plan for Interactions and Information Exchange between the Applicant and FDA during Review of an Original BLA or NME NDA* for additional information on a Formal Communication Plan.

B. Receipt of Application

7. Receive, process, log into CBER's Document Accountability and Tracking System (DATS), and route to the appropriate Office all paper applications and extra reviewer copies. **[DCC] Note:** DCC will route the application based on the product name as reported by the applicant on the Form FDA 356h following current DCC routing procedures.
8. Process electronic applications and notify the appropriate Office per DCC Procedure Guide 22: *Procedure for Processing, Routing, and Storing Electronic Submissions*. **[DCC]**
9. Maintain the original copy of the application (paper and/or electronic) in DCC as an uncirculated record copy. **[DCC]**
10. Determine if the user fee is paid. **[RPM]**
 - a. Consult with the CBER PDUFA Staff (OD/RM), the product office Branch Chief and the product office Division Director as necessary.
 - b. Refer to *SOPP 8406: CBER Processing of PDUFA Application Payments*
 - c. Refer to *Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* for additional information.
11. Notify the CBER PDUFA Staff to perform User Fee verification **[RPM]**
12. Ensure the information on the PDUFA User Fee Cover Sheet (FDA Form 3397) is accurate. Enter the User Fee Identification Number and payment date into the appropriate regulatory database/system for products subject to user fees. **[CBER PDUFA Staff]**
13. Notify the RPM if User Fee payment has not been received. **[CBER PDUFA Staff]**
 - a. If user fee payment is not received within five (5) calendar days of the CBER receipt date:
 - i. Notify the Applicant using the CBER Acknowledgement Letter template, making certain to include the "unacceptable for filing" paragraph. Please refer to CBER's Review Letter

Templates on CBER's Intranet Web page for the most recent approved template. **[RPM]**

- ii. Inform the Review Committee Members to halt review. **[RPM]**

14. Ensure Form FDA 3674 (for clinical trials) was submitted, that all information necessary was provided, and the information is included in the appropriate regulatory database/system. **[RPM]**
 - a. If the form was not submitted, contact the Applicant to request it.
15. Ensure that a Submission Tracking Number (STN) is assigned and that all data, including the characteristic codes and short summary, are entered and all necessary fields are completed in the appropriate regulatory database/system. **[RPM]**
16. Identify other submissions: **[RPM]**
 - a. Identify any submissions referred to by the Applicant (Form FDA 356h and within application).
 - b. Enter these referenced submission numbers in the appropriate regulatory database/system.
 - c. Ensure a check is made with the BITS-PTS and BIRAMS and cross-references are listed in the appropriate regulatory database/system. If appropriate, close the PTS number. Please refer to *SOPP 8114: Administrative Processing of Documents Received Prior to Submitting Investigational or Marketing Submissions (Pre-Applications)* for additional procedures.
 - d. Request a copy of any referenced Drug Master Files to be routed to appropriate reviewers as necessary.
17. Check for Study Data Tabulation Model (SDTM), Analysis Data Model (ADaM) data or Standard for Exchange of Nonclinical Data (SEND). If present, notify CBER's Clinical Data Interchange Standards Consortium (CDISC) representative and request that a CDISC format validation be performed. **[RPM]**
18. Perform CDISC format validation. **[CBER CDISC Representative]** **Note:** if there are errors, inform RPM to notify the Applicant of needed corrections.
19. Notify the Applicant of needed correction; include instructions on how to submit the information. **[RPM]**
20. Review the revision/correction from the Applicant regarding define.xml file, SDTM, ADaM, or SEND dataset formats for CDISC compliance. **[CBER CDISC Representative]**

- 21.** Enter SDTM or ADaM eReview in the appropriate regulatory database/system, as necessary. **[CDISC Reviewer]**
- 22.** Determine if PREA is triggered and notify the office Pediatric Review Committee (PeRC) representative if appropriate. **[RPM]**
 - a. Note:** PREA is triggered when an application for a drug or a biological product is submitted for:
 - i.** a new indication
 - ii.** new dosing regimen (any change in a single dose, maximum daily dose or dosing interval)
 - iii.** new active ingredient (including a new combination)
 - iv.** new dosage form (e.g., vial to transdermal patch)
 - v.** a new route of administration (e.g., subcutaneous to intramuscular)
- 23.** Notify the appropriate supervisors of receipt of the application requesting assignment or confirmation of Review Committee Members, including the following as applicable: **[RPM]**
 - a.** Clinical Reviewer [product office]
 - b.** Clinical Pharmacology Reviewer [product office]
 - c.** Toxicology Reviewer [product office]
 - d.** Developmental Toxicology Reviewer [product office]
 - e.** CMC Reviewer [product office]
 - f.** Office of Compliance and Biologics Quality (OCBQ)
 - i.** DMPQ Reviewer
 - ii.** DMPQ/PRB
 - iii.** APLB Reviewer
 - iv.** BIMO Representative
 - v.** DBSQC or OVRRL/LIB Representative, as appropriate
 - vi.** DMPQ RPM
 - vii.** DMPQ Lead Inspector
 - g.** Office of Biostatistics and Epidemiology (OBE)
 - i.** DB Statistical Reviewer of clinical data
 - ii.** DB Statistical Reviewer of Non-Clinical Data
 - iii.** DE Postmarketing Safety Epidemiological Reviewer
 - h.** Animal Pharmacology Reviewer
 - i.** CMC Inspector
 - j.** Labeling
 - k.** Consult Reviewer (other Center)
- 24.** Assign Review Committee Members; notify RPM. **[Supervisor]**

- 25.** Enter all Review Committee Members in the appropriate regulatory database/system. **[RPM]**
- 26.** Send the name(s) of the product reviewer(s) assigned to review the animal, biological, chemical component/information, if applicable, to the DCC Data Abstraction Team (DAT). **[RPM]**
- Refer to *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements* for additional information.
- 27.** Route application. **[RPM]**
- a.** For electronic applications not in the eMRP, ensure load notifications are sent to appropriate review personnel.
 - b.** For paper applications:
 - i.** Request routing to all Review Committee Members using the Routing Request Screen in RMS-BLA. **[RPM]**
 - ii.** Notify all identified Review Committee Members, including consult reviewers and their supervisors, as appropriate, by email of the routing of paper applications as a reminder to look for the application in their office. **[RPM]**
 - iii.** Route all available review copies in the priority order designated by the RPM. **[DCC]**
- 28.** Initiate review and determine if the application can be filed. See Filing Section below for details. **[Review Committee Members]**
- a.** Notify the RPM if there are issues with components not opening properly, including PDF, SAS transport and other data elements.
 - b.** If the discipline Filing Review Checklist or memo will contain multiple reviews, designate the discipline reviewer responsible for uploading the checklist to the EDR, as appropriate. **Note:** each discipline reviewer may upload a separate Filing Review Checklist.
- 29.** Establish/confirm a draft review schedule, including the following, as applicable: **[RPM, Chair]**
- a.** First Committee Meeting
 - b.** Filing Meeting
 - c.** PeRC meeting
 - d.** Internal Mid-Cycle Meeting
 - e.** Mid-Cycle Communication Telecon

- f. Labeling Meetings
- g. Internal Late-Cycle Meeting
- h. Late-Cycle Meeting (with the Applicant)
- i. Other meetings as necessary (i.e., Advisory Committee, CBER Safety Working Group (SWG) if there are postmarketing requirements)

30. Schedule all review meetings using Microsoft Outlook, inviting all Review Committee Members, supervisors, and senior management as appropriate. **[RPM]** Refer to *R910.02: Attendee Table for BLA/NDA Meetings* for required attendees.

31. Ensure the STN acknowledgment letter is issued, entered in the appropriate regulatory database/system and uploaded into CBER's EDR **[RPM]**

C. Amendments

32. Refer to *SOPP 8405.1: Procedures for Resubmissions for an Application or Supplement* for additional information if the amendment is a resubmission.

33. Receive, process, log into CBER's DATS, and route to the appropriate Office all paper amendments. **[DCC]**

34. Process amendments received electronically and notify the appropriate Office per DCC Procedure Guide 22: *Procedure for Processing, Routing, and Storing Electronic Submissions*. **[DCC]**

35. Characterize the amendment and enter the short summary in the appropriate regulatory database/system; select the Review Committee Members to review the amendment. **[RPM]**

a. If the request for the Proprietary Name Review (PNR) is received separate from the BLA/NDA, notify the Review Committee Members, including APLB, that the amendment is ready for review.

i. Note: The PNR review clock starts when the amendment is received.

ii. Refer to *JA910.02: Proprietary Name Review (PNR) Processing* for additional information.

36. Determine if the amendment should be classified as a major amendment. **[Review Committee Members, Division Director]**

a. Major Amendments:

i. If the amendment is designated as major follow the procedures in *SOPP 8402: Designation of Amendments as Major*.

- ii. Notify the Applicant using the Major Amendment Acknowledgement Letter **[RPM]**
- iii. Enter the information in the appropriate regulatory database/system to extend the review clock. **[RPM]**
- iv. Reschedule previously scheduled meetings to accommodate the review extension date, as applicable **[RPM]**
- v. **Note:** There is only one major amendment allowed per review cycle.

37. Review the amendment. **[Review Committee Members, Chair, RPM]**

C. First Committee Meeting

38. Draft and distribute the agenda in preparation for the First Committee Meeting (if not already provided in the formal meeting invite) no later than 2 days prior to the meeting using the *T 910.15: First Committee Meeting Agenda/Summary* template. **[RPM]**

39. Conduct First Committee Meeting. **[Chair, RPM]**

40. Determine what pre-license or pre-approval Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP) inspections and/or BIMO inspections are necessary; write inspection waiver memorandum(s) if appropriate. **[Review Committee Members]**

- Refer to *SOPP 8410: Determining when Pre-License/Pre-Approval Inspections are Necessary* for additional information.

41. Draft First Committee Meeting summary and identify follow-up activities. Circulate to Review Committee Members for comment. **[RPM]**

42. Review and comment or concur on the First Committee Meeting summary. **[Review Committee Members]**

43. Finalize First Committee Meeting Summary, enter communication into the appropriate regulatory database/system and upload to CBER's EDR. **[RPM, Chair]**

E. Filing Decision

44. Perform review in preparation for the Filing Meeting using the appropriate discipline specific Filing Review Checklist. If there is no discipline specific Filing

Review Checklist, submit review in a Filing Review Memo. **[Review Committee Members]**

- a. Refer to *JA 910.06: Completing a Filing Review* for additional information. The list of discipline specific Filing Review Checklists is found on CBER's Intranet Web page.
- b. Ensure that the application contains the information and data agreed to during the pre-BLA/NDA meeting, except for applications under the PDUFA/BsUFA Programs.
 - i. Applications under the PDUFA Program are allowed to submit stability and clinical safety updates not later than 30 calendar days after receipt of the original application.
 - ii. Applications under the BsUFA Program are allowed to submit stability and clinical safety updates or a limited amount of data from an assessment of a single transition from the reference product to the proposed biosimilar biological product, where applicable, no later than 30 calendar days after receipt of the original application.

45. Complete the appropriate Filing Review Checklist prior to the Filing Meeting. [Review Committee Members]

- a. Notify the Chair, RPM, and supervisors (Branch/Lab Chief, Division Director) of the potential of a Refuse to File (RTF) recommendation. **[Review Committee Members]**
- b. Alert the supervisory chain immediately upon discovering that a RTF recommendation may be made. **[Chair]**
- c. Follow *SOPP 8404: Refusal to File Procedure for Biologic License Applications, New Drug Applications and Efficacy Supplements*.

46. Draft and distribute the Filing Meeting agenda in preparation for the Filing Meeting using regulatory template *T910.16: Filing Meeting Agenda/Summary*. [RPM]

47. Hold Filing Meeting. At the Filing Meeting, each reviewer is expected to discuss the content of the application and present an overview of their relevant portion of the submission. [Review Committee Members]

48. Update the Filing Review Checklist or Filing Review Memo and obtain First Level Supervisor review and signature. [Review Committee Members]

49. Review and sign the Filing Review Checklist or Filing Review Memo; forward to Division Director. [Supervisors]

50. Review and sign the Filing Review Checklist or Filing Review Memo, return to Review Committee Member. **[Division Directors]**
51. Enter Filing Review Checklist or Filing Review Memo in the appropriate regulatory database/system and upload to CBER's EDR. **[Review Committee Members]**
52. Draft the Filing Meeting Summary and document the decision made at the Filing Meeting using information from the Filing Meeting agenda. Circulate to all Review Committee Members for review. **[RPM]**
53. Review and comment on Filing Meeting Summary. **[Review Committee Members]**
54. Finalize the Filing Meeting Summary. **[RPM, Chair]** **Note:** the Chair is the signatory authority.
55. Sign the Filing Meeting Summary **[Chair]**
56. Enter the Filing Meeting Summary in the appropriate regulatory database/system and upload into CBER's EDR. **[RPM]**
57. Draft and circulate the Filing Letter upon concurrence of a filing decision. Please refer to CBER's Review Letter Templates on CBER's Intranet Web page for the most recent approved template. **[RPM]**
 - a. **Note:** if deficiencies are included in the Filing Letter, circulate to the Review Committee Members and supervisors for review.
 - b. Collate revisions into the final version.
58. Sign the Filing Letter; return to RPM. **[Division Director]**
59. Issue the Filing Letter to the Applicant; enter the Filing Letter in the appropriate regulatory database/system and upload to CBER's EDR. **[RPM]**
60. Ask the Applicant if lots for testing could be available should the Review Committee Members find a need to test the product in support of the application (for products subject to lot release). See *SOPP 8408.1: Development of Laboratory Quality Product Testing Plans and Release of Lots as Part of the BLA Approval Process*. **[Chair]**
61. Discuss with the Applicant the need for an Advisory Committee (AC) if applicable. **[Chair, RPM]**
62. Deficiencies Identified (Day-74) Letter, if necessary:

- a. 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 application. **[Review Committee Members]**
- b. Draft a Deficiencies Identified Letter that includes all issues identified in the Filing Meeting but not included in the Filing Letter; circulate to the Review Committee Members. Please refer to CBER's Review Letter Templates on CBER's Intranet Web page for the most recent approved template. **[RPM]**
- c. Review and comment or concur on the Deficiencies Identified Letter. **[Review Committee Members]**
- d. Finalize the Deficiencies Identified Letter; send to Division Director for signature. **[RPM]**
- e. Sign the Deficiencies Identified Letter; return to RPM. **[Division Director]**
- f. Issue the Deficiencies Identified Letter to the Applicant, enter the Deficiencies Identified Letter in the appropriate regulatory database/system and upload to CBER's EDR. **[RPM]**

F. Review Tasks Prior to Mid-Cycle Meeting

- 63.** Confirm the Mid-Cycle Meeting is scheduled via Microsoft Outlook **[RPM]**
- 64.** Confirm that the PeRC meeting is scheduled, as applicable. **[RPM]**
- 65.** Notify Applicant of change in review schedule from expedited to priority if necessary. **[Review Committee Members]**
 - a. Notify Applicant within 3 business days of making the decision. **[RPM]**
 - i. If there is an upcoming meeting with the Applicant, the decision should be discussed during the meeting and included as part of the meeting summary.
 - ii. If the Applicant is notified via telecon, the telecon summary will be sent to the Applicant.
- 66.** Review the Formal Communication Plan agreed to during the pre-BLA/NDA Meeting for any necessary revisions. **[Review Committee Members]**
 - a. Formal Communication Plans are optional so the submission may not have one.

- b. Refer to *R 910.05: Formal Communication Plan for Interactions and Information Exchange between the Applicant and FDA during Review of an Original BLA or NME NDA* for additional information.

67. Lot Release:

- a. See *SOPP 8408.1: Development of Laboratory Quality Product Testing Plans and Release of Lots as Part of the BLA Approval Process* for additional information regarding this process.
- b. Determine if CBER will conduct any testing of the product “in support” of the application. **[Review Committee Members]**
- c. Request that the Applicant identify the lots that will be used for testing if not already stated in the application. Determine if any new instrumentation and/or testing personnel training is needed. Communicate to the Applicant the requirements for submission of samples and lot-specific data. **[RPM, Chair, DBSQC, and PRB]**
- d. Discuss the potential of launch lots with the manufacturer. **[Chair]**
- e. Determine, after collaboration, the post-licensure manufacturer’s lot release protocol requirements for products subject to lot release or surveillance. **[CMC Reviewer/Product Lead, Chair, DPSQC or LIB, Product Release Branch (PRB), Statistical Reviewer]**
- f. Propose any post-licensure CBER confirmatory lot release testing. **[CMC Reviewer/Product Lead and DBSQC or LIB]**
- g. Draft and circulate a Product Testing Plan for review. **[DBSQC or LIB]**

68. Proprietary Name Review:

- a. Ensure the APLB consult proprietary name review (PNR) memorandum is finalized, entered in the appropriate regulatory database/system and uploaded in the EDR. **[APLB]**
- b. Notify the Applicant regarding the PNR decision by the milestone due date, enter communication in the appropriate regulatory database/system and upload into CBER’s EDR. **[RPM]**
- c. Refer to *SOPP 8001.4: Review of Proprietary Names for CBER Regulated Products* and *JA 910.02: Proprietary Name Review (PNR) Processing* for additional information.

69. Inspections:

- a. Confirm BIMO inspection sites; issue inspection assignments to ORA, if applicable. **[OCBQ/BIMO reviewer]**
 - b. Write inspection waiver memorandum(s) if appropriate. **[OCBQ/DMPQ reviewer]**
- 70. Continue review activities in preparation for the Mid-Cycle Meeting. [Review Committee Members]**
- a. Refer to *JA 910.17: BLA/NDA Mid-Cycle Meetings and the Mid-Cycle Communication Telecon* for additional information.
 - b. Each reviewer is expected to document their review of assigned areas in a primary discipline review memorandum that summarizes content, documents the reviewer's assessment, and identifies issues with information and data in the application to date.
 - c. Prepare a Reviewer Report using information taken from the primary discipline review using regulatory template *T 910.09: Reviewer Report*.
 - d. Send Reviewer Report to the RPM (include Chair and reviewer's immediate supervisor (branch/laboratory chief) no later than four (4) business days prior to the meeting.

G. Internal Mid-Cycle Meeting

- 71. Draft the Internal Mid-Cycle Meeting Agenda using regulatory template *T910.06: Mid-Cycle Meeting Agenda/Summary*. Distribute agenda and Reviewer Reports to the Mid-Cycle Meeting attendees no later than two (2) business days prior to the meeting. [RPM]**
- 72. Conduct Internal Mid-Cycle meeting using regulatory template *T 910.06: Mid-Cycle Meeting Agenda/Summary*. [Chair]**
- a. Refer to regulatory job aid *JA 910.17: Mid-Cycle Meetings and the Mid-Cycle Communication Telecon* for additional information.
- 73. Draft the Mid-Cycle Meeting Summary, using information from the agenda sent prior to the meeting; circulate to all attendees. [RPM]**
- a. **Note for products applicable to the PDUFA/BsUFA Programs:** the internal Mid-Cycle Meeting Summary contains the draft agenda for the Mid-Cycle Communication Telecon with the Applicant.
- 74. Review and comment or concur on the Internal Mid-Cycle Meeting Summary. [Review Committee Members]**
- 75. Sign Internal Mid-Cycle Meeting Summary; return to RPM. [Chair]**

76. Finalize Internal Mid-Cycle Meeting Summary; send to product office Division Director for signature. **[RPM]**
77. Sign Mid-Cycle Meeting Summary; return to RPM. **[product office Division Director]**
78. Enter the Mid-Cycle Meeting Summary in the appropriate regulatory database/system and upload into CBER's EDR. **[RPM]**

H. Mid-Cycle Communication Telecon

79. Refer to regulatory reference *R910.02: Attendee Table for BLA/NDA Meetings* for required attendees. **[RPM]**
 - a. Mid-Cycle Communication Telecons apply to applications that qualify under the PDUFA/BsUFA Programs.
 - b. Review Committee Members are included as attendees if they have review discipline issues to discuss.
 - c. Refer to regulatory template *T 910.08: Mid-Cycle Communication (MCC) Telecon Agenda/Summary* for additional information.
80. Provide the Mid-Cycle Communication Telecon agenda (drafted during the Internal Mid-Cycle Meeting) to the Applicant two business days prior to the meeting. **[RPM, Chair]**
81. Hold the Mid-Cycle Communication Telecon within two weeks following the Mid-Cycle Meeting to provide an update on the status of the review of the application. **[RPM, Chair]**
82. Draft and circulate the Mid-Cycle Communication Telecon summary to Review Committee Members ensuring the content is focused only on the status of the review and any agreements or decisions made. **[RPM]**
83. Review and comment or concur, as appropriate, on the Mid-Cycle Communication Telecon Summary. **[Review Committee Members who participated in the Telecon]**
84. Finalize the Mid-Cycle Communication Telecon Summary; send to the Chair for signature. **[RPM]**
85. Sign the Mid-Cycle Communication Telecon summary; return to RPM. **[Chair]**
86. Issue Mid-Cycle Communication Telecon summary to Applicant, enter the information for the Mid-Cycle Communication Telecon in the appropriate regulatory database/system and upload into CBER's EDR. **[RPM]**

I. Review Continued

- 87.** Continue drafting the primary discipline review. **[Review Committee Members]**
- 88.** Send Information requests as needed to facilitate review per *SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Submissions*. **[RPM, Review Committee Members]** **Note:** Per SOPP 8401.1, Information Request communications should not be sent late in the review cycle.
- 89.** Prepare and submit PeRC forms, including: **[Clinical Reviewer, Chair]**
- a.** Pediatric Page
 - b.** Pediatric Template
 - c.** Pediatric Assessment (as appropriate)
 - d.** Pediatric Waiver (as appropriate)
 - e.** Pediatric Deferral (as appropriate)
 - f.** Pediatric Plan (must be included with deferrals)
 - g.** Draft labeling
 - h.** Draft action letter language stating the pediatric disposition
 - i.** Refer to the PeRC Information Web Page located on FDA's Intranet Web page for additional information.
- 90.** Participate in PeRC presentation. **[Clinical Reviewer, Chair]**
- 91.** Ensure the clinical reviewer has addressed the PREA determination (including waiver/deferrals) and the basis for the decision is reflected in the final clinical review memorandum. **[Clinical Reviewer, Chair]**
- 92.** Notify CBER's Safety Working Group (SWG) Office Representative of any Title IX PMRs and/or clinical PMCs as needed. **[RPM, Chair, Clinical Reviewer]**
- 93.** Work with SWG Executive Secretary to schedule presentation at the SWG meeting, if needed. **[Office SWG Representative]**
- 94.** Draft the proposed PMR and/or clinical PMC topics and supportive documentation; send to SWG Office Representative, if applicable. **[Chair, RPM, Clinical Reviewer, OBE DE Reviewer]**
- 95.** Send the proposed PMR and clinical PMC language and supportive documentation to SWG Executive Secretary. **[SWG Office Representative]**
- 96.** Present proposed PMRs or clinical PMCs at SWG Meeting. Make revisions to the proposed PMRs/PMCs as necessary based on SWG feedback. **[Chair, RPM, Clinical Reviewer, OBE DE Reviewer]**
- 97.** Notify the Applicant of all proposed PMRs, clinical and non-clinical PMCs; request the Applicant's feedback or concurrence. **[Chair, RPM, Clinical Reviewer, OBE DE Reviewer]**

- 98.** Provide final version of agreed upon PMR/PMC language to Review Committee Members, Office PMR/PMC Coordinator and supervisor. **[RPM]**
- 99.** Complete the draft Product Testing Plan; send to Chair for review. **[DBSQC Chair, CMC Reviewer]**
- 100.** Ensure Pharmacovigilance Plan is adequate, if applicable. **[OBE Epidemiological Reviewer]**
- 101.** Ensure Establishment Inspection Waiver Memorandum(s) have been completed, entered in the appropriate regulatory database/system and uploaded to the EDR, as needed. **[DMPQ, CMC Reviewers]**
- 102.** Ensure Environmental Assessment (EA) has been reviewed and that review is documented, if applicable. **[product office RPM]**
- 103.** Ensure that the Components Information Table is included in the discipline review memo. **[CMC Reviewer]**
- 104.** Ensure Categorical Exclusion (CE) claim is documented in the discipline review memo **[DMPQ Reviewer]**
- 105.** Inspections
- a.** Perform inspections if not already completed. **[Review Committee Members, Inspection Team]**
 - b.** Enter inspection memo(s) date(s) in the appropriate regulatory database/system and upload into the EDR if facility inspections were performed. **[DMPQ Lead Inspector]**
 - c.** Send appropriate sections of the EIR to the respective inspection lead and finalize the report. **[Lead Inspector, CMC Inspector]** **Note:** EIRs must be completed regardless of final action.
 - d.** 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]**
- 106.** Lot release
- a.** Identify post-licensure lot release protocol review(s) per SOPP 8408.1. **[DBSQC or LIB Representative, CMC Reviewer & Lab Chief, OCBQ/DMPQ/PRB Chief]**

- b. Develop Data Collection Plan(s) for Lot Release Protocols. [**Lot Release Protocol Reviewer(s)**]
- c. Enter Data Collection Plan(s) into the appropriate regulatory database/system and upload into the EDR. [**Lot Release Protocol Reviewer(s)**]

107. Labeling

- a. Schedule labeling meeting(s) as needed. Refer to *SOPP 8412: Review of Product Labeling* for additional information. [**RPM**]
- b. Prepare labeling meeting summary and enter in the appropriate regulatory database/system. [**RPM**] **Note:** if appropriate, revised labeling may substitute for a meeting summary.
- c. Communicate with Applicant regarding labeling decisions. [**RPM**]

J. Late-cycle Meeting for Applications Subject to the PDUFA/BsUFA Programs

108. Update the Reviewer Report from the Mid-Cycle Meeting; send to the RPM and Chair 4 days prior to the Internal Late-Cycle Meeting. [**Review Committee Members**]

109. Draft the Late-Cycle Review Committee Memo in preparation for the Internal Late-Cycle Meeting. [**Chair, RPM**]

- Refer to regulatory job aid *JA 910.11: Late-Cycle Meetings* for additional information.

110. Prepare and send the Late-Cycle Internal Meeting agenda, including the Review Committee Memo, to the Review Committee 2 days prior to the Internal Late-Cycle Meeting using regulatory template *T 910.10: Late-Cycle Meeting (LCM) Internal (Pre) Meeting Summary*. [**Chair, RPM**]

- Refer to regulatory reference *R 910.02: Attendee Table for BLA/NDA Meetings* for required attendees.

111. Hold Internal Late-Cycle Meeting. [**Chair, RPM, Review Committee Members**]

112. Draft the Internal Late-Cycle Meeting Summary, using the agenda sent prior to the internal meeting; circulate to all meeting attendees. [**RPM**]

113. Review and comment or concur on the Late-Cycle Internal Meeting Summary. **Note:** the Meeting Materials and agenda for the Late-Cycle Meeting with the

- Applicant is part of the meeting summary. **[Review Committee Members, Internal Meeting Attendees]**
- 114.** Finalize the Internal Late-Cycle Meeting Summary and Meeting Materials, send to Chair. **[RPM]**
 - 115.** Review and concur on Internal Late-Cycle Meeting Summary and Meeting Materials, send to Division Director. **[Chair]**
 - 116.** Sign the Internal Late-Cycle Meeting Summary and the Meeting Materials Cover Sheet, send to RPM. **[Division Director]**
 - 117.** Issue Late-Cycle Meeting Materials to Applicant no later than 10 calendar days (or 2 calendar days for expedited reviews) prior to the meeting. **[RPM]**
 - 118.** Enter Internal Late-Cycle Meeting Summary and Late-Cycle Meeting Materials in the appropriate regulatory database/system and upload to the EDR. **[RPM]**
 - 119.** Late-Cycle Meeting with Applicant
 - a.** Conduct the Late-Cycle Meeting with the Applicant **[RPM, Chair]**
 - **Note:** This meeting is not intended to discuss the pending regulatory decision on the application.
 - b.** Discuss with the Applicant whether additional data or analysis that may be submitted will be reviewed by the Agency in the current review cycle and, if so, whether the submission will be considered a major amendment and trigger an extension of the user fee goal date. **[Chair, RPM, Review Committee Members]**
 - c.** Draft the Late-Cycle Meeting Summary using the information from the agenda sent to the Applicant prior to the meeting and regulatory template *T910.12: Late-Cycle Meeting Summary*. **[RPM, Chair]**
 - d.** Circulate the draft Late-Cycle Meeting Summary to all CBER/FDA Late-Cycle meeting attendees and supervisors; ensure that there is agreement on the content. **[RPM]**
 - e.** Review and comment or concur on the Late-Cycle Meeting Summary. **[Review Committee Members, Supervisors]**
 - f.** Finalize Late-Cycle Meeting Summary, send for signature. **[RPM]**
 - g.** Sign Late-Cycle Meeting Summary, send to RPM. **[Chair, Division Director]**

- h. Send the Late-Cycle Meeting Summary to the Applicant. **[RPM]**
- i. Enter the Late-Cycle Meeting Summary in the appropriate regulatory database/system and upload into CBER's EDR. **[RPM]**

K. Review Wrap-up

- 120.** Finalize the Primary Discipline Review Memo(s) and any review addendums, as appropriate, and route to supervisory chain for signature. **[Review Committee Members]**
- 121.** Perform secondary discipline review of any Primary Discipline Reviews and any review addendums; send to Division Director for signature **[Team Lead, Supervisor]**
 - a. Review the primary discipline review memorandum(s).
 - b. If the decision is to concur with the recommendation, a signature on the primary discipline review memorandum is sufficient.
 - c. If the decision is to non-concur, document the decision and the reasons in a separate review memorandum. Sign the non-concur memorandum prior to forwarding to Division Director for signature. **Note:** if a non-concurrence memo was written, notify the RPM and Chair.
- 122.** Sign the Primary Discipline Review Memo(s) after the Secondary Discipline Review was signed by supervisor; return to Review Committee Member. **[Division Director]**
- 123.** Determine if a press release is warranted. **[Chair, RPM]**
 - **Note:** a press release may be needed for an important indication or a novel product.
- 124.** Contact the Office of Communication, Outreach, and Development (OCOD), Division of Communication and Consumer Affairs (DCCA) Consumer Affairs Branch (CAB) if decision was made that a press release is appropriate. **[Chair, RPM]**
- 125.** Enter the Final Discipline Review Memo and all addendums in the appropriate regulatory database/system and upload into the EDR; notify the RPM and Chair. **[Review Committee Members]**
- 126.** Finalize EIRs, ensuring the narrative report, supervisory endorsement, and other communications are entered in the appropriate regulatory database/system and uploaded to CBER's EDR. **[Inspection Team]**

- 127.** Verify Lead Inspector closes out inspection(s) and uploads the FACTS endorsement(s) into the EDR, when possible. **[DMPQ RPM] Note:** if the inspection cannot be closed prior to approval then the final action must result in a CR.
- 128.** Send Inspection Tab, including the EIR with exhibits and attachments, and any other paper communications and amendments, to DCC according to *DCC Procedure Guide #11: Procedure for Filing Pre-License/Pre-Approval Inspection Material*. **[Inspection Team]**
- 129.** Enter date(s) of field management directive (FMD-145) letters that were issued for closed inspections into the appropriate regulatory database/system. **[OCBQ/DIS]**
- 130.** Perform Complete Response (CR) or approval process per the process below. **[Review Committee Members]**

L. Complete Response (CR) Actions

- 131.** Provide discipline review memorandum and CR letter-ready comments, approved by the supervisory chain, to Chair and RPM. **[Review Committee Members]**
- 132.** Include any compliance issues and/or pending status of inspections in the CR letter. **[RPM, DMPQ Reviewer]**
- 133.** Draft and circulate CR letter to Review Committee Members, all appropriate Review Office Branch Chiefs and Division Directors for review and agreement. Please refer to CBER's Review Letter Templates on CBER's Intranet Web page for the most recent approved template. **[RPM]**
- 134.** Review and comment or concur on CR letter. **[Review Committee Members, Supervisors]**
- 135.** Collate and finalize revisions for the CR letter, send to Division Director for signature. **[RPM, Chair]**
- 136.** Sign CR letter; send to RPM. **[Division Director]**
- 137.** Ensure all documents or communications and all other relevant information are entered in the appropriate regulatory database/system and uploaded into CBER's EDR. **[Review Committee Members]**
- 138.** Notify the Applicant of the CR, issue the letter, enter in the appropriate regulatory database/system and upload to the EDR. **[RPM]**

M. Approval Actions

- 139.** Ensure product dating has been determined (expiration dates have been established), if applicable. **[Chair, CMC Reviewer]**
- 140.** Ensure the labeling comments were communicated to the Applicant and final labeling issues were addressed. **[RPM]**
- 141.** Draft the Summary Basis of Regulatory Action (SBRA) using regulatory template *T 910.07: Summary Basis of Regulatory Action (SBRA)*; circulate to Review Committee Members for comment. **[Chair]**
- Refer to *JA 910.16: Processing SBRA*s for additional information.
- 142.** Review and comment or concur on the SBRA. **[Review Committee Members]**
- 143.** Collate revisions to SBRA; route to supervisors. **[Chair]**
- 144.** Review and comment or concur on the SBRA. **[Supervisors]**
- 145.** Draft the press release, if needed, and coordinate with the Center Press Release Office in OCOD/DCCA/CAB. **[Chair]**
- 146.** Draft and circulate the Approval Letter to the Review Committee Members. Please refer to CBER's Review Letter Templates on CBER's Intranet Web page for the most recent approved template. **[Chair, RPM]**
- 147.** Review and comment or concur on the Approval Letter. **[Review Committee Members]**
- a. If the Approval Letter contains any PMR/PMCs, circulate the mature draft to the Office PMR/PMC Coordinator and Center PMR/PMC Liaison for review. **[Chair]**
- 148.** Prepare the electronic Action Package (eAP) and circulate as appropriate. Perform quality control check on documents that were uploaded into CBER's EDR. **[RPM]**
Note: this is not the Action Package for Posting.
- 149.** Obtain lot release clearance. **[RPM]**
- 150.** Submit final Product Testing Plan to DBSQC or LIB Division Director, Office Director (or designee), DMPQ Director, and Center Lab Quality Manager (CLQM) for signature. **[Chair, DBSQC or LIB Representative]**
- 151.** Enter final Testing Plan information in the appropriate regulatory database/system and upload to CBER's EDR. **[DBSQC or LIB Representative]**

- 152.** Obtain compliance check. **[RPM, DMPQ RPM]** Refer to regulatory job aid *JA900.10: Compliance Check Requests* for additional information.
- 153.** Obtain point of contact for Action Package for Posting requirement from OCOD/Division of Disclosure and Oversight Management (DDOM)/Electronic Disclosure Team (EDT). Refer to *SOPP 8401.7: Action Packages for Posting* for additional information. **[RPM]**
- 154.** Send final draft label revision to Applicant (includes all final Review Committee Member's comments). **[RPM]**
- 155.** Email the Officer/Employee list to all Review Committee Members and those involved in the approval process using regulatory template *T 910.02: Officer/Employee List Email*. **[RPM]**
- 156.** Respond to the Officer/Employee list email. **[Review Committee Members]**
- 157.** Finalize SBRA; send to Office Director for signature. **[Chair]**
- 158.** Ensure all communications were entered in the appropriate regulatory database/system and uploaded to CBER's EDR. **[Review Committee Members]**
- 159.** Send the final draft Approval Letter and eAP to all appropriate Review Offices, Branch Chiefs, and Division Directors for review and agreement. **[RPM, Chair]**
- 160.** Review and comment or concur on the final eAP and Approval Letter. **[appropriate review offices, Branch Chiefs, and Division Directors]**
- 161.** Send final eAP, including Transmittal Memo using *T910.01: Transmittal Memo* and Approval Letter for signature. **[RPM]**
- 162.** Sign final eAP, Transmittal Memo, SBRA and Approval Letter. **[Office Director(s)]**
- a. Signatory Authority for SBRA and Approval Letter**
 - i.** Original BLAs (for existing U.S. License Number)/NDAs:
 - a) Office Director or Deputy Office Director, product office
 - ii.** Original BLAs (for new U.S. License Number)
 - a) Office Director or Deputy Office Director, product office **AND**
 - b) Office Director or Deputy Office Director, OCBQ
- 163.** Communicate approval to the Applicant; issue Approval Letter. **[Chair, RPM]**

- 164.** Provide DMPQ/PRB and DIS/PSB with a copy of the approval letter so that PRB may complete the lot release process and PSB may share the Approval Letter with ORA. **[RPM]**
- 165.** Prepare Action Package for Posting per *SOPP 8401.7: Action Package for Posting* and regulatory checklist *C 910.01: Action Package for Posting*. **[RPM]**
- Ensure documents for posting are appropriately selected (using the post to Web checkbox) in RMS-BLA.
- 166.** Provide the Transmittal Memo, the Approval Letter, the Package Insert, and the SBRA (in Word format attached to the certified pdf) in an email to OCOD/Division of Communication and Consumer Affairs (DCCA)/Communication Technology Branch (CTB). **[RPM]**
- 167.** Complete the Review Completion Process in the appropriate regulatory database/system. **[RPM]**
- 168.** Provide Notification of Release to the Applicant for any Launch Lots as appropriate. **[DMPQ review committee member]**
- 169.** Approval files: **[RPM]**
- Assemble paper files for submission to DCC or
 - Complete E-FAP for electronic applications.
- 170.** Return any documents (submission file) that need information corrected in RMS-BLA. **[DCC]**
- 171.** Make any necessary corrections in RMS-BLA. **[Review Committee Members]**
- For communications not entered prior to the 30 day lockdown, prior approval from the immediate supervisor is necessary for any entries to RMS-BLA.
 - Refer to regulatory job aid *JA 910.08: Lockdown of Applicant Submissions and CBER Correspondence for Marketing Submissions* for additional information.

N. After Action Activities

- 172.** Conduct Internal After-Action Meeting to analyze how the review process worked. **[RPM, Review Committee Members]**
- a. Refer to regulatory reference *R 910.02: Attendee Table for BLA/NDA Meetings* for attendees.

- b.** Refer to regulatory job aid *JA 900.12: After Action Activities for BLAs and NDAs in the PDUFA Program* for additional information

173. Submit After-Action Meeting summary to the Associate Director for Review Management (ADRM). **[RPM]**

VIII. Appendices

N/A

IX. References

A. References below are located on CBER's Intranet Web Page (unless otherwise noted)

1. Document Control Center Procedures

- a.** DCC Procedure Guide 8: Procedure for Filing Final Action Packages Containing Paper FDA Correspondence for Marketing Applications – Including Multiple Products
- b.** DCC Procedure Guide 11: Procedure for Filing Pre-License/Pre-Approval Inspection Material
- c.** DCC Procedure Guide 22: Procedure for Processing, Routing, and Storing Electronic Submissions

2. Regulatory Checklists

- a.** C 910.01: Action Package for Posting Checklist
- b.** C910.02: 10 Month BLA Checklist
- c.** C 910.04: PDUFA Checklist for Original BLAs and Efficacy Supplements
- d.** Discipline Specific Filing Review Checklists

3. Regulatory Job Aids

- a.** JA 820.02: Dating of CBER Correspondence

- b.** JA 900.01: Unique Ingredient Identifier (UNII) Code
- c.** JA 900.10: Compliance Check Requests
- d.** JA 900.12: After Action Activities for BLAs and NDAs in the PDUFA Program
- e.** JA 910.01: Manufacturing Facility Data Entry
- f.** JA 910.02: Proprietary Name Review Processing
- g.** JA 910.06: Completing a Filing Review
- h.** JA 910.08: Lockdown of Applicant Submissions and CBER Correspondence for Marketing Submissions
- i.** JA 910.11: Late-Cycle Meetings
- j.** JA 910.12: Conducting the Late-Cycle Meeting
- k.** JA 910.16: Processing SBRA's
- l.** JA 910.17: BLA/NDA Mid-Cycle Meetings and the Mid-Cycle Communication Telecon

4. Regulatory References

- a.** R 810.04: Meeting Information
- b.** R 810.05: Electronic Submissions: CBER Rejection Process by Document Type
- c.** R 910.02: Attendee Table for BLA/NDA Meetings
- d.** R 910.04: Expedited Review Information

- e. R 910.05: Formal Communication Plan for Interactions and Information Exchange between the Applicant and FDA during Review of an Original BLA or NME NDA**

5. Regulatory Templates

- a. T 910.01: Transmittal Memo**
- b. T 910.02: Officer/Employee List Email**
- c. T 910.06: Mid-Cycle Meeting Agenda/Summary**
- d. T 910.07: Summary Basis of Regulatory Action (SBRA)**
- e. T 910.08: Mid-Cycle Communication (MCC) Telecon Agenda/Summary**
- f. T 910.09: Reviewer Report**
- g. T 910.10: Late-Cycle Meeting (LCM) Internal (Pre) Meeting Summary**
- h. T 910.11: Late-Cycle Meeting Materials**
- i. T 910.12: Late-Cycle Meeting Summary**
- j. T 910.15: First Committee Meeting Agenda/Summary**
- k. T910.16: Filing Meeting Agenda/Summary**

6. Review Template Letters

7. PerC Information Page

8. Standard Operating Policies and Procedures (SOPPs)

- a. SOPP 8301: Receipt and Processing of Master Files**
- b. 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

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>

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

<https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/federalfooddrugandcosmeticactfdca/default.htm>

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

<https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm>

d. Food and Drug Administration Modernization Act (FDAMA) of 1997

<https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAAct/FDAMA/default.htm>

e. Food and Drug Administration Safety and Innovation Act (FDASIA)

<https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAAct/FDASIA/default.htm>

f. Public Health Service Act

<https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/ucm148717.htm>

g. Pediatrics

i. Pediatric Research Equity Act (PREA)

[Full-text of Pediatric Research Equity Act of 2007 \(PREA\) \(PDF - 383KB\)](#)

ii. Pediatric Product Development Information

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

iii. Best Pharmaceuticals for Children Act (BPCA)

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf>

h. User Fee Acts

i. Biosimilar User Fee Act (BsUFA)

<https://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm>

ii. Generic Drug User Fee Amendments (GDUFA)

<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm>

iii. Medical Device User Fee Amendments (MDUFA)

<https://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFee/default.htm>

iv. Prescription Drug User Fee Act (PDUFA)

<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

2. Guidance Documents

a. Guidance for Industry: Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172134.pdf>

b. Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Submissions under Section 745A(a) of the FD&C Act

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384686.pdf>

c. Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Standardized Study Data

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>

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

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf>

- e.** Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products (April 2005)

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf>

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

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf>

3. Standard Operating Policy and Procedures

- a.** SOPP 8001.2: Accessing the FDA Lists of Disqualified and Restricted Clinical Investigators, Debarred Individuals, and Firms Under the FDA Application Integrity Policy

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm061224.htm>

- b.** SOPP 8001.4: Review of Proprietary Names for CBER Regulated Products

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm063086.htm>

- c.** SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>

- d.** SOPP 8104: Documentation of Telephone Contacts with Regulated Industry

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079463.htm>

- e.** SOPP 8114: Administrative Processing of Documents Received Prior to Submitting Investigational or Marketing Applications (Pre-Application)

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079476.htm>

- f.** SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Submissions

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073078.htm>

- g.** SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073088.htm>

- h.** SOPP 8401.7: Action Package for Posting

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm211616.htm>

- i.** SOPP 8402: Designation of Amendments as Major

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073461.htm>

- j.** SOPP 8404: Refusal to File Procedure for Biologics License Applications

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073474.htm>

- k.** SOPP 8404.1: Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File Over Protest)

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073478.htm>

- l.** SOPP 8406: CBER Processing of PDUFA Payment Information

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073495.htm>

- m.** SOPP 8405.1: Procedures for Resubmissions of an Application or Supplement

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073490.htm>

- n.** SOPP 8407: Compliance Status Checks

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073498.htm>

- o.** SOPP 8408.1: Development of Laboratory Quality Testing Plans and Release of Lots as Part of the BLA Approval Process

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm245350.htm>

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

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073506.htm>

- q.** SOPP 8411.1: Administrative Handling and Review of Annual Reports for Approved Biologic License Applications (BLAs)

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073509.htm>

- r.** SOPP 8412: Review of Product Labeling

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073510.htm>

- s.** SOPP 8413: Postmarketing Commitment Related Submissions – Administrative Handling, Review, and CBER Reporting

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm223772.htm>

- t.** SOPP 8415: Procedures for Developing Postmarketing Requirements and Commitments

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073519.htm>

4. FDA Forms

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

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf>

- b.** Form 3397: PDUFA User Fee Coversheet

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm>

- c. 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))

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf>

IX. History

Written/Revised	Approved	Approval Date	Version Number	Comment
Dixon	Christopher Joneckis, PhD	September 27, 2017	8	Revised to incorporate new procedures
Rehkopf RMCC Working Group	Robert A. Yetter, PhD	April 18, 2013	7	Revised to accommodate new user fee authorizations and updates from other SOPPs and to add NDAs
Linda Dixon	Robert A. Yetter, PhD	April 30, 2007	6	Revised to include information on PTS.
RMCC	Robert A. Yetter, PhD	March 9, 2007	5	Incorporates changes to describe lot release activities associated with product review and to include additional review activities
RMCC	Robert A. Yetter, PhD	May 11, 2003	4	Changes incorporating new SOPP 8104.3: Filing Action: Communications Options
RMCC	Robert Yetter, PhD	Oct 2, 2002	3	Changes accommodating PDUFA III and other updates
RMCC	Robert A. Yetter, PhD	Feb 22, 2000	2	Incorporates changes necessitated by publication of BLA final rule (64 FR 56441) and Biostatistics & Epidemiology change from Division to Office
		Sept 10, 1997	1	Original