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# Manual of Standard Operating Procedures and Policies

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## Regulatory - License Applications

### Administrative Processing of Biologics License Application Supplements (BLSs) [Except Blood, Blood Components, and Source Plasma]

SOPP 8401.2

Version #3

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#### 1. Purpose

This document provides instructions to Center for Biologics Evaluation and Research (CBER) staff on the administrative handling of supplements to approved applications, except those involving blood, blood components, or Source Plasma.

#### 2. Definitions

See Appendix 1 for a list of abbreviations and acronyms used in this SOPP.

#### 3. Background

On October 7, 1997, the final rule, "Changes to an Approved Application" (62 FR 39890) became effective. This final rule amended the biologics regulations for reporting of changes to an approved application under 21CFR 601.12 in order to reduce reporting burdens on applicants holding licenses approved by the CBER. The final rule also amended the corresponding drug regulations under 21 CFR 314.70. Two documents were published at the same time; "Changes to an Approved Application: Biological Products;" and "Changes to an Approved Application: for Specified Biotechnology and Specified Synthetic Biological Products," to provide guidance to industry on how specific changes should be reported.

Changes to the manufacturing process or facility for biological products were to be reported as supplements to the applicant's product license application (PLSs) or establishment license application (ELsS) in accordance with this regulation, or in the form of an annual report to the product license application (PLA) for changes that were deemed to have minimal potential to have an adverse effect. Changes to the manufacturing process or facility for specified biotechnology and specified synthetic biological products, as defined in 21 CFR 601.2(c), were to be reported as supplements or in an annual report to the applicant's biologics license application (BLA).

On October 20, 1999, the final rule "Biological Products Regulated Under Section 351 of the Public Health Service Act; Implementation of the Biologics License; Elimination of Establishment and Product Licenses" (64 FR 56441) was published. The rule became effective December 20, 1999. On the effective date of the

final rule, a 10-month transition period began. During this period, manufacturers, where applicable (i.e. of products not defined under 21 CFR 601.2(c)), could submit PLSs and ELSs. However, once received, these submissions were to be processed administratively by CBER as BLSs.

In addition, the final rule provided that applicants who already had an approved ELA and PLA for a product would not be required to make any submission to CBER to comply with the new requirements. The approved PLA for the product together with portions of the approved establishment license application (ELA) relevant to the new requirements for the BLA were deemed to constitute an approved BLA under the new regulations.

#### 4. Policy

It is the policy of CBER that all changes submitted to approved license applications under 21 CFR 601.2 will be processed as either supplements or annual reports to BLAs, as appropriate. The procedures set forth in this SOPP will be used to supplement previously issued CBER SOPPs (see references below) that describe administrative handling and review of license supplements.

Note: Procedures for processing and reviewing annual reports are specified in CBER SOPP 8411.1, "Changes to an Approved Application - Administrative Review and Handling of Annual Reports".

Office-specific SOPPs will address additional responsibilities of the regulatory project manager (RPM), reviewers, and other staff.

#### 5. Procedures

##### A. Pre-BLS Activities

- i. The RPM assigned to the Investigational New Drug Application (IND) or Biologic Product Application (BLA) will, when scheduling permits, be the primary contact for information on submission of the BLS and will coordinate pre-BLS activities.
- ii. The RPM will schedule end-of-phase 2, and/or pre-phase 3 and pre-BLS meetings (as specified by CBER SOPP 8101.1, "Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants"), if such meetings are requested by the sponsor, and will ensure appropriate participation by representatives of all review disciplines that will be involved in the BLS. Participants should include, as appropriate, product and clinical reviewers and reviewers from the Division of Manufacturing and Product Quality (DMPQ), the Division of Biostatistics (DB), Office of Biostatistics and Epidemiology (OBE), the Bioresearch Monitoring (BiMo) branch, and consult reviewers from other Offices or Centers within the Agency. If the subject of the pre-BLS meeting is to address facility issues only, DMPQ will process the request for the meeting.
- iii. If the BLS will involve a new clinical indication, a new dosage form, or a substantial change in the package insert (e.g., revised pediatric use or geriatric use sections), requests for end-of-phase 2 and/or pre-phase 3 and pre-BLS meetings and discussions will be processed as amendments to the appropriate IND. If no IND exists, these requests and associated meeting minutes will be processed as BLA Correspondence. The request should be assigned a second level STN.
- iv. Issues that relate to DMPQ review responsibilities will be forwarded to the DMPQ reviewer for response.
- v. The RPM will take the lead in identifying reviewer needs and coordinating any electronic submission filing. All electronic filings will be coordinated with the pertinent electronic submission coordinators (ESCs) in the product Office, DMPQ, and DB as well as with representatives of the Document Control Center (DCC), the Office of Information Management (OIM) and the Center electronic submission coordinator (CESC). All interested parties should be notified as early as possible of a potential electronic filing to ensure their readiness to process it efficiently. Refer to "Guidance for Industry, Providing Regulatory Submissions in

Electronic Format - Biologics Marketing Applications (BLA, PLA/ELA, and NDA)" and "Guidance for Industry, Providing Regulatory Submissions in Electronic Format - General Considerations.

- vi. Arrangements will be made by the RPM to obtain the necessary copies of pertinent volumes of the BLS for all reviewers, including those from DB and BiMo. The RPM will notify the Document Control Center (DCC) of the expected arrival date and size of the supplement. The RPM will contact DCC to make delivery arrangements for large submissions and supply DCC with sponsor contact information. DCC considers a large submission to be one that exceeds a total of 50 volumes (including copies) or about 5 cubic feet.

## B. BLS Receipt and Processing

- i. FDA Form 356h should be submitted with all correspondence to CBER. This information will aid in routing the submission to the appropriate division for processing.
  - ii. All BLSs (and extra reviewer copies) will be received in DCC, logged in, and routed to the appropriate Office based on the product name [and supplement type if indicated] as reported by the applicant on the FDA Form 356h. Electronic submissions will be processed per established procedures and the applicable ESC(s) notified. The original of the submission (paper and/or electronic) will be maintained in DCC as an uncirculated archival copy. The RPM will request additional copies from the sponsor as needed.
- a. Supplements to be administered (and Chaired) by DMPQ include:
1. "Establishment Description" supplements ("non-specified" products);
  2. Chemistry Manufacturing and Control (CMC) supplements for introduction of new products into multi-use facility areas;
  3. CMC Supplements for facility changes (except testing facilities) that do not include manufacturing process changes; and
  4. CMC supplements regarding changes to sterility, endotoxin, and pyrogen test methods and facilities (not involving changes in the manufacturing processes or materials tested).

For each of the above situations, the RPM will be provided by DMPQ. The committee will include reviewers from all affected Product offices if the change impacts the product, including changes to manufacturing processes as well as facility-only changes that are supported by product data.

- b. Supplements to be administered 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 sterility, endotoxin, and pyrogen testing).

For each of these situations, the RPM will be provided by the product review office. A DMPQ reviewer will be on the committee for supplements regarding cleaning validation, campaigning

and changeover procedures, changes regarding aseptic processing steps, new container-closures, and new validations involving existing equipment (e.g. a larger load in lyophilizers). A DMPQ reviewer should also be on the committee for any supplement for which a pre-approval inspection is necessary (see SOPP 8410).

- iii. Upon receipt of the BLS, the RPM will ensure that a Submission Tracking Number (STN) is assigned in the Regulatory Management System - Biologics License Application (RMS-BLA) and the STN assignment letter is issued. The RPM will provide DCC a listing of the committee members to receive review copies and ensure routing occurs. For electronic submissions, the above steps will be performed on the document in the Electronic Document Room (EDR). For supplements affecting multiple products, an STN will be assigned for each product and the STN assignment letter will list each STN and product. A copy of the signed letter with a concurrence page will be sent to DCC for filing.
  - a. The RPM will ensure that the required data, including establishment information, are entered into RMS-BLA. A determination of the user fee status will be made and a copy of the user fee cover sheet FDA Form 3397) should be sent to the Regulatory Information Management Staff (RIMS), per SOPP 8406: Verification of User Fee Data Sheet and Payment.
  - b. The RPM will ensure that the proper reporting category is assigned in accordance with 21 CFR 601.12 (Changes to an Approved Application).
  - c. The RPM will request reviewer assignments in accordance with Office specific SOPPs. The RPM will also notify the reviewers' Branch or Laboratory chiefs of the incoming submission. All reviewers, including those in DMPQ, OBE, and BiMo, should be listed as committee members in RMS-BLA.
- iv. Each reviewer will evaluate the pertinent information captured in RMS-BLA for accuracy and completeness upon receipt of the BLS. If additions and/or corrections are necessary, the reviewer should advise the RPM and the RPM will ensure that the changes are made.

### C. Review Committee and Supplement Review

- i. The full review committee should be invited to all committee meetings.
- ii. All review disciplines will contribute to a filing decision. Refusal to file a BLS may be based on deficiencies found in any section of the submission per SOPP 8404: "Refusal to File Guidance for Product License Applications and Establishment License Applications" and 21 CFR 601.12. The RPM will ensure that the filing action is taken and a letter is sent to the sponsor (the filing action may be addressed in the STN assignment letter.)

Note: When a decision is made to file a supplemental application, the applicant must be notified in the filing letter or within 14 days of the 60 day filing date of either 1) potential filing issues or 2) no potential filing issues identified during the filing review. Refer to SOPP 8401.3 Filing Action: Communication Options, for communication procedures.

- iii. The RPM will confirm that BiMo assignments have been issued when required. The BiMo reviewer will forward the final report to the RPM for inclusion in the file.
- iv. If necessary, the RPM will confirm with the DMPQ reviewer that pre-approval inspection teams have been identified and the inspection(s) initiated in a timely manner, in accordance with SOPP 8410: "Determining When Pre-License/ Pre-Approval Inspections are Necessary."
  - a. the inspection team should include both product and DMPQ reviewers from the committee. The DMPQ team member will take lead responsibility for the inspection and notify the Program

- Inspection Branch (PIB), Office of Compliance and Biological Quality (OCBQ) when the inspection is scheduled.
- b. The PIB will notify the appropriate Office of Regulatory Affairs (ORA) contact(s) according to the SOP "CBER/ORA Joint Inspection Program."
  - c. Upon completion of the inspection and resolution of inspection issues, the PIB will prepare an inspection package including the the Establishment Inspection Report (EIR), exhibits, response(s), and the EIR close-out memorandum. This package, accompanied by an EIR document index memorandum will be be forwarded to the RPM for RMS-BLA data entry and inclusion in the BLS file. [See Document Control Center Procedure #11: Procedure for Filing Pre-license/Pre-approval Inspection Material.]
- v. The RPM will ensure that all appropriate information and milestones are recorded in RMS-BLA, that milestones are being met, and that all outstanding issues or disagreements are resolved and documented in the archival file. Each committee member will promptly forward the original of all internal documentation of meetings, telephone conversations, reviews, etc., to the RPM for data entry and submission to DCC for filing. The RPM ensures that summaries of formal meetings with sponsors are sent to the sponsor and copies are sent to DCC for filing.
  - vi. Regulations [21 CFR 25.20-25.31] require submission of an Environmental Assessment (EA) or request for Categorical Exclusion (CE) for certain actions. It is CBER's policy that a request for a CE generally needs to be submitted if there is a potential increase in the amount of product or production by-products being released into the environment. Examples include supplements for a new manufacturing facility, new or expanded indications, increased production scale, duplicate process trains, etc. The majority of Changes Being Effectuated (CBE) and Changes Being Effectuated - 30 Days (CBE-30) supplements would not require inclusion of an EA or request for a CE. The RPM will determine whether an EA or CE has been submitted. If an EA or CE was not submitted but may be needed, the RPM will consult with DMPQ.
    - a. The EA will be reviewed by the assigned or consult DMPQ reviewer who will also be responsible for preparing and signing the Finding Of No Significant Impact (FONSI) when such a finding is appropriate. The FONSI will be sent through and signed by the DMPQ division director before forwarding to the RPM for inclusion in the file.
    - b. If the applicant applies for and is granted a categorical exclusion from the EA, a review memo for the categorical exclusion, prepared by the DMPQ reviewer, will take the place of the FONSI.
  - vii. The RPM will coordinate the issuance of all Information Request (IR), Discipline Review (DR), and Complete Response (CR) letters. Draft IR, DR, and CR letters should be circulated by email for 72-hour comment to allow review by all committee members and their supervisors.
    - a. Information Request and Complete Response letters will be issued over the signature of the Office Director designate of the office that is administratively processing the BLS. Review and concurrence should be obtained from the appropriate individuals in each office with review responsibility. The responsible Division Director will sign IR and CR letters for clinical-only supplements. DR letters will be signed by Office-specific procedures.
    - b. Letters involving Clinical, CMC, *and* establishment issues will be prepared by the product office RPM and will require review and/or concurrence from the appropriate individuals in the product office and the DMPQ division director and branch chief. For blood components, letters will be prepared by the chairperson and will require review and/or concurrence from appropriate individuals in the product office.

- c. If the only issues are establishment related and a product office is administratively processing the BLS, the letter will be prepared by DMPQ. The letter will require concurrence from the DMPQ branch chief and division director and appropriate individuals in the product office before signing by the Office Director designate with product responsibility.

#### D. Approval Activities

- i. The RPM will ensure that the compliance status check is initiated in accordance with SOPP 8407: Compliance Status Checks, at least 30 days prior to the expected action date, where possible. This will routinely be done by the DMPQ reviewer, as he/she will know when all inspectional issues have been adequately addressed. The request and response will be sent to the RPM for data entry and inclusion in the archival file. When there is no DMPQ reviewer on the committee, the RPM will request the compliance check.
- ii. For products subject to lot release, the RPM will check with Product Release Branch (PRB), DMPQ to determine if there are any lots in support of the supplement and their testing status.
- iii. The RPM will prepare the Licensing Action Recommendation Memorandum (LARM) and the approval letter in accordance with Office-specific SOPPs. The signoff routing for the LARM should include the individuals listed on the form. The letter will be signed in accordance with Office-specific SOPPs with routing through the branch chief and Division Director, DMPQ, if the committee includes a reviewer from DMPQ.
- iv. Approximately two weeks prior to approval of supplements for new indications or ones for which there is significant public interest, the RPM will notify the Office of the Center Director, the Office of Communication, Training and Manufacturers Assistance (OCTMA), and the FDA Press Office of the expected approval.
- v. The RPM will ensure that a quality control check of the archival file has been performed, per office specific SOPPs, on all information captured and entered into RMS-BLA. The RPM will send the completed supplement, including the signed approval letter with concurrence page, to DCC for filing. If applicable, the Summary Basis for Approval (SBA) or cover memorandum from the SBA Equivalent reviews, and FONSI, will be filed in the archive submission behind the LARM and forwarded with the complete submission to DCC for filing.
- vi. The RPM will ensure that, *for all supplements*, copies of the dated approval letter are distributed to the Director of the appropriate product Office, the Director of the Applications Division, members of the review committee and their respective Division Directors, RIMS, and if subject to CBER lot release, PRB, DMPQ. Copies of the signed approval letter, with concurrence page, and the FONSI (if applicable) will be sent to the Regulatory Information Specialist in DMPQ for filing in the official "blue" License file.
- vii. In addition, *for supplements involving revised labeling (e.g., modifications to indications, dosage forms, routes of administration, adverse reaction sections, etc.)* the RPM will ensure that copies of the dated letter and the final draft package and patient (if applicable) inserts are distributed to the Director of the Applications Division, OCTMA, the Chief of the Advertising and Promotional Labeling Branch (APLB), OCBQ, and the Director DE, OBE. When approving a new or expanded clinical indication, the RPM will ensure that a copy of the final draft labeling, or final labeling if available, is sent to the Office of the Center Director and the FDA Press Office; and that a copy of the SBA (or equivalent) is sent to OCTMA.

#### E. Withdrawal Activities for Pending BLSs

- i. The RPM will process the withdrawal request.

- ii. The RPM will prepare the withdrawal letter and will ensure routing and sign-off in accordance with Office-specific SOPPs. The supplement withdrawal letter will bear the signature of the Office Director-designate of the Office that is administratively processing the supplement.
- iii. The RPM will ensure that a quality control check has been performed on all information captured and entered into RMS-BLA. The RPM will send the supplement, including all manufacturing submission, CBER generated correspondence and a copy of the signed withdrawal letter, with concurrence page to DCC for filing, following DCC Procedure Guide 8 and 9.
- iv. The RPM will ensure that the withdrawal letter is distributed to the product applications Division Director, and the DMPQ Director. A copy of the signed withdrawal letter will be sent to the Regulatory Information Specialist in DMPQ for filing in the official License file.

**6. Appendix 1**

[Abbreviations](#)

**7. Effective Date**

May 11, 2003

**8. History**

<b>Comment/Revision</b>	<b>Approved By</b>	<b>Approval Date</b>	<b>Version Number</b>	<b>Comment</b>
S. Risso, RMCC	Robert Yetter, PhD	7/26/2002	1	Original
Leonard Wilson, RMCC	Robert Yetter, PhD	10/1/2002	2	Changes to accommodate PDUFA III and other updates
Leonard Wilson, RMCC	Robert Yetter, PhD	5/11/2003	3	Changes to accommodate incorporation of SOPP 8401.3, Filing Action: Communication Options

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