

SOPP 8411.1: Administrative Handling and Review of Annual Reports for Approved Biologics License Applications (BLAs)

Version #4

Effective Date: June 1, 2011

I. PURPOSE

The purpose of this document is to describe the policies and procedures for receipt and handling of Annual Reports to Biologics License Applications (BLAs) submitted to the Center for Biologics Evaluation and Research (CBER) as required by 21 CFR 601.12(d) and 601.12(f)(3). This document also describes the procedures for review of these reports.

II. SCOPE

This SOPP is applicable to BLA Annual Reports submitted to CBER, excluding postmarketing requirements/commitments Annual Reports. Please refer to *SOPP 8413: Postmarketing Requirement/Commitment Related Submissions – Administrative Handling, Review, and CBER Reporting* for further information.

III. BACKGROUND

- A.** On July 24, 1997, the final rule, "Changes to an Approved Application," was published in the Federal Register. This revision to 21 CFR 601.12 established three reporting categories for changes to product, manufacturing processes, personnel, facilities, equipment and labeling. One of the reporting categories established is the Annual Report, a mechanism not previously used for licensed products.
- B.** The changes to an approved BLA required to be reported in an Annual Report are changes in the labeling, product, production process, quality controls, equipment, facilities or responsible personnel that have minimal potential to have an adverse impact on the identity, purity, potency, strength or quality of the product as they may relate to its safety or efficacy. For changes reported in Annual Reports, as with all changes, the applicant is responsible for performing any necessary studies and tests to assure that there has been no adverse effect on the identity, purity, potency, strength or quality of the product.

IV. DEFINITIONS

- A.** **21 CFR 601.12(d)(1)** - Changes to be described in an annual report (minor changes). Changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the

identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product shall be documented by the applicant in an annual report submitted each year within 60 days of the anniversary date of approval of the application. The Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, may approve a written request for an alternative date to combine annual reports for multiple approved applications into a single annual report submission.

- B. 21 CFR 601.12 (f)(3)** – Labeling changes requiring submission in an Annual Report: an applicant shall submit any final printed package insert, package label, container label, or Medication Guide ... incorporating the changes as provided in 601.12(d)(1)
- C. Administrative File** - the file or files containing all documents pertaining to a particular administrative action, including internal working memoranda, and recommendations (21 CFR 10.3).
- D. Regulatory Management System-Biologics Licensing Application (RMS-BLA)** - the CBER database used to track biologic license submissions; including licensed device applications
- E. Inspection Follow-up Memorandum** – Memo sent to CBER’s Office of Compliance and Biologics Quality (OCBQ), Division of Inspections and Surveillance (DIS) requesting inspectional follow-up of an issue during the next biennial inspection or directed inspection after review of a submission. The follow-up issues are not critical enough to require a supplement or supporting information, but require verification by inspectors.

V. POLICY

- A.** All Annual Reports for changes to an approved application are submitted to CBER through CBER’s Document Control Center (DCC) or electronically through the Food and Drug Administrations (FDA) Electronic Submission Gateway (ESG).
- B.** A complete administrative file consists of the applicant’s submissions, CBER reviews and communications with the applicant, and communications internally with other FDA staff.
- C.** CBER will perform an initial review to determine whether the changes being reported are appropriate for an Annual Report. This initial review should be completed within 90 calendar days of the receipt of the Annual Report. If changes are inappropriately reported in the Annual Report, the applicant will be notified in writing as soon as possible.
- D.** Annual Reports should be completely reviewed within 180 calendar days of receipt, the review documented in CBER’s regulatory database (RMS-BLA) and imported into CBER’s Electronic Document Room (EDR).

- E. Generally, it is CBER's policy to allow applicants to address problems found during review of Annual Reports without unnecessary interruption of product supply. However, if circumstances warrant, the agency may require that the change be immediately discontinued or follow-up action may be taken.
- F. The status of postmarketing requirements or commitments should not be included in Biologics License Application Annual Reports. Please refer to *SOPP 8413: Postmarketing Requirement/Commitment Related Submissions – Administrative Handling, Review, and CBER Reporting* for further information.
- G. The applicant should submit labeling in Structured Product Labeling (SPL) format if their current labeling was never previously submitted in SPL, regardless if there are any changes to the labeling (21 CFR 601.14(b)).

VI. RESPONSIBILITIES

A. Document Control Center (DCC)

- 1. Processes and maintains all Annual Report documents in the same manner as other biologics license submissions

B. Branch Chief

- 1. Participates in discussions and decisions pertaining to inappropriately reported changes, as appropriate
- 2. Concurs with review memo

C. Regulatory Project Manager

- 1. Coordinates the review of the Annual Report
- 2. Ensures the Annual Report is routed to other reviewers, Divisions, or Offices as necessary
- 3. Contacts the applicant by telecon if postmarketing requirements or commitments were included and requests resubmission of that portion of the data in another appropriate submission
- 4. Ensures that reviews are performed and all CBER communications are documented according to CBER policies and procedures
- 5. Serves as the point of contact for all correspondence with the applicant concerning the Annual Report
- 6. Participates in telephone notification to applicant of inappropriate categorization of changes
- 7. Issues Inappropriate Use of Annual Report letter, as appropriate

8. Verifies that any labeling submitted is in SPL format

D. Reviewer

1. Performs an initial review of the Annual Report, within 90 calendar days, for appropriate categorization of changes
2. Determines if postmarketing requirements or commitments were included (rather than submitted separately). If these were included, notifies the RPM so a communication can be initiated
3. Performs a complete review of the Annual Report, including labeling, within 180 calendar days
4. Participates in discussions and decisions pertaining to inappropriately reported changes, engaging the Branch Chief, as appropriate
5. Sends letter ready comments to the RPM for inclusion in the Inappropriate Use of Annual Report letter to the applicant, as appropriate
6. Documents review, including recommendations for actions needed (e.g. inspection, letter to applicant), and a statement that the Annual Report is either satisfactory or not satisfactory, or equivalent language
7. Prepares an Inspection Follow-up Memo identifying issues in the review memo that should be referred for evaluation during the next inspection or during a directed inspection, if appropriate
 - a. Copies supervisor on the Inspection Follow-Up Memo
 - b. Sends the Inspection Follow-up Memo to OCBQ/DIS
8. Documents CBER communications, including review memos and, if applicable, the Inspection Follow up Memo in RMS-BLA and imports all documents into CBER's EDR.

E. Office of Compliance and Biologics Quality (OCBQ)

1. Division of Manufacturing and Product Quality (DMPQ):
 - a. Reviews the Annual Report for facility or manufacturing information
2. Division of Inspections and Surveillance (DIS), Program Surveillance Branch:
 - a. Adds inspectional issues from the Inspection Follow-up Memo to the next Team Biologics biennial inspection plan (or for blood facilities, to the District Office's next inspection plan) and
 - b. Coordinates inspectional activities as needed

3. Division of Case Management (DCM)
 - a. Coordinates further compliance activities as needed

VII. PROCEDURES

- A. Receive and process all Annual Reports per the same procedures as other biologic license submissions receiving a second level STN. For additional information, see *SOPP 8401.2: Administrative Processing of Biologics License Application Supplements* and *DCC Procedure Guide 22: Procedure for Processing, Routing and Storing Electronic Submissions*. [DCC]
- B. Ensure that the Annual Report is logged into RMS-BLA as a second level STN upon receipt of the Annual Report in the review office [RPM]
- C. Determine appropriate review disciplines and routing of the Annual Report including other reviewers, Divisions, or Offices as necessary [RPM]
 1. Route a copy of the Annual Report to OCBQ/DMPQ if the Annual Report contains facility or manufacturing information, with the exception of Annual Reports for blood and blood components
 2. Route Annual Reports for blood and blood components to the Blood and Plasma Branch, Division of Blood Applications, Office of Blood Research and Review (BPB/DBA/OBRR). These annual reports should not be routed to OCBQ. [DCC]
 3. Refer to *SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements* for additional information on other Office review responsibilities
 4. Refer to regulatory job aid *JA 900.02: SPL Content of Labeling* and *SOPP 8412: Review of Product Labeling* for additional information on labeling submitted in the Annual Report
- D. Submission routing [RPM]
 1. For paper submissions, request DCC hard copy routing via the “Routing Request” feature in RMS-BLA.
 2. For electronic submissions, the RPM will forward the eLoad Notification email.
- E. Perform an initial review of the Annual Report, within 90 calendar days, for appropriate categorization of changes [Reviewer]
 1. If the changes being reported are appropriate for an Annual Report, no action is needed regarding categorization. (proceed to F. below)

2. Determine the alternatives available to the applicant to address the incorrect categorization if a change is found to be inappropriately reported in the Annual Report **[reviewer, RPM, Division Director, all appropriate review staff from other Divisions/Offices]**
 - a. The following should be considered in these deliberations:
 - i. Whether or not the reported change may have an adverse impact on the safety, purity, or potency of the product
 - ii. CBER's intent to allow applicants to correct these problems without unnecessary interruption of product supply, if this is in the best interest of the public health
 - iii. The appropriate reporting category and data needed for review
 - iv. Circumstances that might require the change to be immediately discontinued
 - v. Any necessary follow-up action, such as product recall or a directed inspection
3. Contact OCBQ/DIS to discuss what action would be appropriate if a determination is made that follow-up action by OCBQ is necessary. For example, follow-up action may be a directed inspection of routine or high priority, or forwarding the information to FDA's Office of Regulatory Affairs (ORA) for review at the next scheduled inspection. **[Review Committee]**
4. Consult with OCBQ/Division of Case Management (DCM) if regulatory action is warranted **[OCBQ/DIS]**
5. Notify the applicant by telephone immediately if the Annual Report contains inappropriately reported changes or information **[RPM]:**
 - a. Advise the applicant that the inappropriately reported change requires the submission of a supplement
 - b. Advise the applicant of the type of supplement required
 - c. Notify the applicant of any additional actions necessary to address the incorrect filing or if there is additional information needed to complete the review
 - d. Advise the applicant if postmarketing requirements or commitments were included as they should be submitted in a separate submission
 - e. Document the telecon in RMS-BLA and import the telecon record into CBER's Electronic Document Room (EDR)

6. Send letter ready comments that include justification of resubmission and reporting category to RPM for the “Inappropriate Use of Annual Report” letter **[Reviewer]**
 7. Notify the applicant in writing of the inappropriate category designation and actions necessary to address the incorrect categorization as soon as possible after telephone notification using the “Inappropriate Use of Annual Report” template letter located on CBER’s Regulatory Letter Template Intranet Web page). **[RPM]**
 - a. OCBQ/DMPQ will issue the letter, after consultation with the review committee, if it contains *only* facility or manufacturing changes
 - b. OBRR/DBA/BPB will issue the letter for facility or manufacturing changes if the Annual Report is for blood and blood components
 - c. The Product Office will issue the letter for other product or labeling changes requiring a supplement
- F.** Prepare a review memorandum within 180 calendar days stating that the Annual Report is satisfactory or not satisfactory, and include recommendations for actions needed (e.g., inspection, letter to applicant) **[Reviewer]**
1. Generally the review memo consists of:
 - a. A summary or list of changes reported
 - b. CMC reviewers should document changes to components/components information per *SOPP 8401.5: Processing of Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*
 - c. A statement that the changes are satisfactory or not satisfactory or, equivalent language
 - d. Review issues identified and an explanation of their resolutions
 - e. Any action required
- G.** Prepare an Inspection Follow-up Memorandum, if applicable. **[Reviewer]**
1. The memo should clearly identify the applicant, product, facility, STN, date of the Annual Report and issues to be covered during the next biennial inspection or any significant issues for which a directed inspection is necessary
 2. Provide the memo to OCBQ/DIS, Program Surveillance Branch by email to the Branch’s inspection account, cberinspections@fda.hhs.gov.

- H.** Document the review memorandum and, if applicable, the Inspection Follow-up Memo in RMS-BLA, import the memo into the EDR, and notify the RPM [**Reviewer**]
- I.** Document any additional communication with the applicant in RMS-BLA before the 180 calendar day deadline. [**Reviewer, RPM**]
- J.** Complete the administrative file according to the following DCC Procedure Guides, as appropriate: [**RPM**]
 - 1.** DCC Procedure Guide 8: Procedure for Filing Final Action Packages Containing FDA Correspondence for Marketing Applications
 - 2.** DCC Procedure Guide 9: Procedure for Filing Multiple Product Final Action Packages Containing FDA Correspondence for Marketing Applications
 - 3.** DCC Procedure Guide 10: Procedure for Filing a Marketing Submission that does not Require CBER Correspondence
 - 4.** DCC Procedure Guide 23: Procedure for Filing Action Packages Containing Electronic FDA Communication for Marketing Applications
- K.** File Annual Reports in appropriate license application folder after review [**DCC**]
 - After the Annual Report is filed in the license application folder, it may be requested from DCC at any time for reference (e.g., prior to an inspection).

VIII. APPENDIX

N/A

IX. REFERENCES

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

- 1.** DCC Procedure Guide #8: Procedure for Filing Final Action Packages Containing FDA Correspondence for Marketing Applications
- 2.** DCC Procedure Guide #9: Procedure for Filing Multiple Product Final Action Packages Containing FDA Correspondence for Marketing Applications
- 3.** DCC Procedure Guide #10: Procedure for Filing a Marketing Submission that does not Require CBER Correspondence
- 4.** DCC Procedure Guide #22: Procedures for Processing, Routing and Storing Electronic Submissions
- 5.** DCC Procedure Guide #23: Procedure for Filing Action Packages Containing Electronic FDA Communication for Marketing Applications
- 6.** Regulatory job aid JA 900.02: SPL Content of Labeling

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

B. References located on Internet Web pages

1. 21 CFR 601.12(d); 21 FR 301.12 (f) (3)
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>
2. SOPP 8413: Postmarketing Commitment Related Submissions – Administrative Handling, Review and CBER Reporting
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm223772.htm>
3. SOPP 8401.2: Administrative Processing of Biologics License Application Supplements
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073082.htm>
4. SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073088.htm>
5. SOPP 8412: Review of Product Labeling
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073510.htm>
6. Final Rule “Changes to an Approved Application” (62 FR 39901, July 24, 1997)
<http://www.gpoaccess.gov/fr/advanced.html>

X. HISTORY

Comment/Revision	Approved By	Approval Date	Version Number	Comment
Linda Silvers Linda Dixon	Robert Yetter, PhD	May 16, 2011	#4	Revised procedures and title
Leonard Wilson	Robert Yetter, PhD	October,21 2001	#3	Corrections of header in Appendix 1

Jules Meisler	Robert Yetter, PhD	October 16, 2001	#2	Modifications to address changes in DCC procedures, organizational names and add a review closeout memorandum.
RMCC	Rebecca Devine	March 10, 1999	#1	Original Document