SOPP 8408.1: Development of Laboratory Quality Product Testing Plans and Release of Lots as Part of the BLA Approval Process

Version: 2
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I. Purpose

A. This SOPP provides procedures for Center for Biologics Evaluation and Research (CBER) staff for:

1. The review of manufacturer's lot-specific testing data,

2. The conduct of any CBER testing of sample(s) submitted pursuant to 21 CFR 601.2(a) *applications for biologics licenses; procedures for filing* and

3. The activities conducted prior to approval needed to prepare CBER for any post-approval monitoring of product.

II. Scope

A. This procedure covers CBER-regulated products during the biologics license application (BLA) review process.

III. Background

A. In accordance with 21 CFR 601.2(a), to obtain a biologics license under section 351 of the Public Health Service Act for any biological product, the manufacturer shall submit an application to the Director, Center for Biologics Evaluation and Research (CBER). Manufacturers are required to submit various information including information and data related to representative samples of the product to demonstrate manufacturing consistency and ability to meet specifications. As such, CBER evaluates the summaries of results and also determines whether to perform any testing of its own as part of the product evaluation process.

B. In accordance with 610.2(a), samples of any lot of licensed product together with the results of applicable tests may at any time be required to be sent to the Director, Center for Biologics Evaluation and Research. Lots shall not be distributed until the lot is released by the Director, Center for Biologics Evaluation and Research. CBER will not generally require post-licensure lot release except when deemed necessary for the safety, purity or potency of the product.

C. CBER's decision whether to require lot release post-licensure and, if determined to be necessary, how to evaluate a product for distribution post-licensure is

initially determined during the BLA review process. This may include decisions on the test methods and test results to be submitted by the manufacturer in a lot release protocol, as well as a determination of the need for any confirmatory testing to be conducted by CBER.

IV. Definitions

A. Confirmatory Testing – Testing of regulated products conducted by CBER in order to verify results reported by the manufacturer.

B. Data Collection Plan – the plan for how data will be collected and the analysis performed to monitor manufacturer's lot release test results over time.

C. Exempt from Lot Release – Condition of licensure whereby the manufacturer is not required to submit lot-specific protocols or samples to CBER for review. **Note:** The manufacturer may distribute lots without a release notification from CBER. Summary lot release data may be submitted and reviewed in Annual Reports or in lot-specific protocols depending on the terms of the license.

D. Laboratory Quality Database (LQDB) – Database of information supporting the Laboratory Quality System

E. Laboratory Quality System (LQS) program – Organizational structure, policies, procedures, processes and resources needed to conduct regulatory testing activities in a secured and controlled environment using appropriately qualified and validated methods for generating data supportive of Center regulatory activities.

F. Launch Lots – Product lots available for distribution into interstate commerce at the time of BLA approval. Launch lots have also been known as exhibit lots. **Note:** Launch lots are not a requirement for approval.

G. Lot Release – Condition of licensure whereby the manufacturer is required to submit lot-specific protocols and possibly samples to CBER for review. **Note:** The manufacturer may not distribute individual lots until receiving a release notification from CBER.

H. Lot Release Program – CBER activities, resources, and processes engaged in fulfilling CBER's responsibilities under 21 CFR 610.2, including products subject to either Lot Release or Surveillance.

I. Lot Release Protocol – Manufacturer's summary document sent to CBER for the purpose of obtaining CBER's permission to release a lot of product into

distribution, per 21 CFR 610.2(a), or for CBER review under a surveillance program; typically containing lot-specific manufacturing information and testing results.

J. Lot Release System (LRS) – Database of information supporting the Lot Release Program.

K. Laboratory Quality Product Testing Plan – Documentation of CBER's current approach to evaluating a licensed product including the circumstances under which CBER would or would not conduct testing.

L. Regulatory Testing Activities - Laboratory activities performed by CBER consisting of:

1. Official testing (as defined in CBER's Lab Quality Policy Manual) – testing that has a direct impact on a regulatory position (i.e. licensure of new products, routine release of products into the marketplace, approval of changes to licensed products, compliance action, or formal international collaboration and
2. Associated activities – development and evaluation of reference materials/standards, studies evaluating a manufacturer's reference standard, or assay.

M. Surveillance Plan – Condition of licensure, usually conferred by the approval of a supplement to the BLA, whereby the manufacturer is required to submit a specified sampling of lot-specific protocols, samples and periodic summary reports of released lots to CBER for review. **Note:** The manufacturer may distribute lots at their own risk without waiting for a release notification from CBER.

N. Testing Lab – for purposes of this SOPP, any CBER laboratory that tests regulated product, pre- or post-licensure, for the purposes of licensing, Lot Release or Surveillance.

V. Policy

A. The timely review of test results and lot release protocols are an important part of the approval process for biological products. Early communication and collaboration, both internally and with manufacturers, is essential during the approval process with respect to review of lot release protocols, sample requirements and the availability of LQS program- compliant testing procedures for performance of confirmatory In-Support testing at CBER.

B. Failure of the applicant to identify lot numbers of biological products which are

available for submission In-Support of licensure to CBER in the BLA may be considered as a basis for issuance of a Refusal to File letter to the applicant per 21 CFR 601.2.

C. Protocols and lot samples should be submitted to CBER only after a CBER issued submission tracking number (STN) has been assigned to the application. In consideration of tight license review timelines, samples may be requested ahead of the Lot Release Protocol submission for individual lots. It is preferable for manufacturers to wait until CBER has reviewed the manufacturer's submitted lot release protocol template prior to submitting completed Lot Release Protocols.

D. Testing performed In-Support of licensing and routine lot release is conducted under the CBER LQS program.

E. CBER develops a Laboratory Quality Product Testing Plan describing the requirements for post-market evaluation and lot release of each product including a description of how and under what conditions CBER intends to test samples.

F. Per 21 CFR 610.2(a), CBER may at any time require sample and protocol submission for the purposes of Lot Release.

G. Once implemented, Laboratory Quality Product Testing Plans are reviewed and updated periodically, as appropriate.

VI. Responsibilities

A. Center Lab Quality Manager (CLQM):
- **1.** Reviews the Laboratory Quality Product Testing Plan.
- **2.** Confirms that the Laboratory Quality Product Testing Plan is complete and meets the requirements of the CBER LQS program.
- **3.** Approves the Laboratory Quality Product Testing Plan.

B. Chemistry, Manufacturing, and Controls (CMC) Reviewer/Product Lead:
- **1.** Proposes, with justification, any need for CBER to perform testing In-Support of the submission.
- **2.** Reviews both manufacturer and any CBER lot-specific testing data.
- **3.** Proposes and discusses as appropriate:
  - **a.** The test methods and product specifications to be included in manufacturer's post-licensure lot release protocols;
  - **b.** The role and identity of post-licensure lot release protocol reviewer(s);
  - **c.** The content for a Data Collection Plan, and
  - **d.** CBER's confirmatory testing post-licensure.

C. Committee Chair:

1. Communicates to the applicant any requirements for samples and testing data, if appropriate.

D. Division of Biologic Standards and Quality Control (OCBQ/DBSQC) or Laboratory of Immunobiochemistry (OVRR/DBPAP/LIB):

1. Summarizes Review Committee discussions and decisions on whether CBER will test samples In-Support of a submission.
2. Facilitates discussions on:
   a. The development of the Laboratory Quality Product Testing Plan;
   b. Test methods and product specifications to be included in manufacturer's post-licensure lot release protocol(s);
   c. Role and identification of post-licensure lot release protocol reviewer(s); and
   d. Any potential post-licensure confirmatory testing performed by CBER.
3. Routes the finalized Laboratory Quality Product Testing Plan for approval.
4. **Note:** DBSQC staff performs these responsibilities for all products other than allergenic products in which case LIB staff fulfills these responsibilities.

E. Division of Manufacturing and Product Quality (DMPQ/OCBQ) Director:

1. Reviews the Laboratory Quality Product Testing Plan.
2. Confirms that DMPQ/Product Release Branch (PRB) is prepared to receive the product post-licensure.
3. Approves the Laboratory Quality Product Testing Plan.
4. Releases appropriately cleared launch lots at the time of licensure.

F. Product Release Branch (OCBQ/DMPQ/PRB):

1. Serves as the Center Sample Custodian [21 CFR 600.2(c)] and as manager of the Lot Release Program (Branch Chief).
2. Provides notification to Committee Chair and RPM that samples and protocols have arrived.
3. Provides the necessary processing of samples and lot release protocols as part of the approval process.
4. Clears launch lots for release at the time of approval.
5. Reviews format for post-licensure manufacturer's lot release protocol template.
6. Discusses role and identity of any post-licensure lot release protocol reviewer(s).
7. Prepares, as needed, to receive and manage product post-licensure.

G. Product Office Director (or designee):

1. Decides, based on the recommendations of the Review Committee and Committee Chair and the outcome of Center-wide negotiations:

a. Whether the product will be subject to Lot Release or Exempt from Lot Release;
b. Any CBER testing activities to be included in the Laboratory Quality Product Testing Plan;
c. Role and identity of any post-licensure lot release protocol reviewer(s) (accomplished through the product office Lab/Branch Chiefs).

2. Creates a separate review memo stating the reasons for disagreement if the Office Director does not concur with the Review Committee recommendation.
3. Approves the final Laboratory Quality Product Testing Plan prior to the approval of a new product or product class.
4. Provides for or ensures that resources are sufficient for testing assignments stipulated in the Laboratory Quality Product Testing Plan.
a. Confirms the plan represents an appropriate use of public resources per the CBER LQS program, FDA Staff Manual Guide 2350.1 and Office of Personnel Management circular A-123, "Management's Responsibility for Internal Control."

H. Protocol Reviewer(s):
1. Develops and finalizes the Data Collection Plan.

I. Regulatory Project Manager (RPM):
1. Ensures that communications between the Review Committee Members and the manufacturer or between the Review Committee Members and other Center representatives are recorded and included in the file.
2. Ensures the appropriate language describing any need for post- licensure lot release responsibilities are included in the Approval Letter.

J. Review Committee Members (including DBSQC or LIB representative):
1. Proposes and negotiates whether approval of the submission should be conditional based on manufacturer participation in the Lot Release Program.
2. Determines any need for CBER testing of samples submitted In-Support in of the submission.
3. Recommends whether CBER should perform confirmatory testing post-licensure.

K. Statistician:
1. Discusses as appropriate:
a. Product specifications to be included in manufacturer's post- licensure lot release protocols, and
b. Content for a Data Collection Plan.

L. Testing Lab(s):

1. Performs product testing as requested, In-Support or post- licensure.
2. Reviews results of testing.
3. Reviews protocol.

M. Testing Lab Division Director:

1. Reviews the Laboratory Quality Product Testing Plan.
2. Confirms testing labs are prepared and resourced to conduct assigned testing.
3. Approves the Laboratory Quality Product Testing Plan.

VII. Procedures

- Activities described may be performed concurrently as outcomes of steps in one section may influence steps in other sections.

A. For all products

1. Determine whether this product should be subject to Lot Release or Exempt from Lot Release. Refer to *R 900.02: Reviewer Considerations for Post-Market Product Assessment* for additional information. **[Review Committee Members]**

B. For Lot Released products

1. Discuss whether CBER should maintain testing methods for the post-marketing evaluation of production lots for release under 21 CFR 610.2. Refer to *R 900.01: Reviewer Considerations for CBER Product Testing Post-Licensure* for additional information. **[CMC Reviewer/Product Lead and DBSQC or LIB representative]**
2. Determine what type(s) of sample(s), i.e., bulk, final container, etc., and from what stage(s) of manufacturing samples should be submitted. **[CMC reviewer, Testing Labs, PRB]**

C. CBER Testing In-Support of approval of the submission

1. Consider not later than the Mid-Cycle meeting whether CBER will conduct testing on samples of the product. Refer to *R 900.03: Reviewer Considerations for CBER Product Testing In-Support of Licensing Action* for additional information. **[Testing Labs, DBSQC or LIB representative, RPM, CMC reviewer, Chair]**
2. Summarize in meeting minutes the factors which the Review Committee considered while making the decision on whether to request CBER testing In-Support of the submission, including any disagreements. **[DBSQC or LIB representative]**
3. If testing will occur:

a. Request the manufacturer to provide samples for testing In-Support of the submission. Determine from the manufacturer if these samples represent launch lots. **[Chair]**

i. If the "*In-Support samples*" represent launch lots to be released by CBER for distribution after approval of the submission, request samples be submitted to the Sample Custodian.

ii. If the "*In-Support samples*" do not represent launch lots to be released by CBER for distribution after approval of the submission (Exempt products or samples for In-Support testing only) request samples be sent directly to the testing lab(s).

b. Request manufacturer's lot-specific testing data be provided as an amendment to the submission, if not already included. **[CMC Reviewer, DMPQ]**

c. Request the Sample Custodian release samples, if the samples are from launch lots, to the testing labs by emailing PRB-201 form (supplied by the Sample Custodian upon sample receipt) to the "CBER Sample Request" mailbox. **[Chair]**

d. Perform testing as agreed. **[Testing Labs]**

e. Prepare the Testing In-Support Results memo using Regulatory Template *T 910.03: Testing In-Support Results.* **[Testing Labs]**

i. Communicate unanticipated or unusual test results to the manufacturer. **[CMC Reviewer/Product Lead, Chair, and Testing Lab]**

ii. In the case of unanticipated or unusual test results, if samples were distributed from PRB, report results to the PRB Chief. **[Testing Lab]**

f. Enter the test results memo into RMS–BLA and import into CBER's EDR. **[Testing Labs]**

g. Record testing outcome(s) in LRS if the samples are from launch lots. Refer to the LRS User Guide for additional information. **[Testing Labs]**

h. Review CBER Testing In-Support Results memo. **[CMC Reviewer/Product Lead]**

4. Review manufacturer's lot-specific testing data. **[CMC Reviewer/Product Lead]**

D. Manufacturer's Lot Release Protocol Template

1. This section does not apply to products Exempt from Lot Release

2. Request a lot release protocol template be submitted as an amendment to the BLA. **[CMC Reviewer/Product Lead, DBSQC or LIB representative, PRB]**

3. Review the lot release protocol template not later than the Late-Cycle internal meeting. **[CMC Reviewer/Product Lead, Chair, DBSQC or LIB representative, PRB, Statistical Reviewer]**
    a. Lot release protocol templates should include the name of the product, assay method, test date, specification and result; other information may be requested.
    b. Refer to *R900.04: Reviewer Considerations for Manufacturer's Lot Release Protocol Template* for additional information.
4. Facilitate discussion among Lab/Branch chiefs with product responsibility, CMC Reviewer/Product lead, and PRB on the role and identity of post-licensure lot release protocol reviewers. **[DBSQC or LIB representative]**
5. Define the Data Collection Plan(s) the lot release protocol reviewer(s) will use post-licensure to trend manufacturer's data as reported in lot release protocols. **[Lot Release Protocol Reviewer(s)]**
6. Enter the Data Collection Plan(s) into the EDR**. [Lot Release Protocol Reviewer(s)]**
    a. **Note:** Not part of the action package for posting for original BLAs.
7. Update LRS as needed to reflect lot release protocol requirements and reviewer(s). **[PRB]**

E. Laboratory Quality Product Testing Plans

1. Draft the Laboratory Quality Product Testing Plan by the Mid-Cycle Meeting using *LQS Document ID 000172: Laboratory Quality Product Testing Plan Blank Template.* **[DBSQC or LIB representative]**
2. Negotiate within the Center the details of the Laboratory Quality Product Testing Plan. **[Committee Chair, DBSQC or LIB representative, CMC Reviewer/Product Lead, Office Director or designee, Testing Lab(s) as appropriate]**
3. Prepare and route the finalized Laboratory Quality Product Testing Plan for approval. **[Chair, DBSQC or LIB representative]**
4. Review and approve the Laboratory Quality Product Testing Plan. **[Testing Lab Division Director, Product OD , DMPQ Division Director, CLQM]**
5. Update the LQDB document control records; enter the Laboratory Quality Product Testing Plan into the RMS-BLA, import into the EDR. **[DBSQC or LIB representative**]
    a. **Note:** Not for posting as part of the action package
6. Include appropriate language in the Approval Letter describing any post-licensure needs, as determined by the product Office Director, for the manufacturer to submit lot release protocols and, if appropriate, samples. Refer to CBER's Review Template Letters on CBER's Intranet Web page for the most recent approved template. **[RPM]**

F. Launch Lots

1. **Note**: This section does not apply to products exempt from lot release.
2. **Note**: This section will apply if launch lots are intended to be released at the time of approval.
3. Discuss with the manufacturer by the Mid-Cycle review, any potential launch lots and lot release protocols. **[Chair]**
4. Consider, during the Mid-Cycle meeting, if samples and manufacturer's lot-specific testing data provided In-Support of the submission represent suitable launch lots and lot release protocols. **[Chair]**
5. Verify that launch lots are cleared for release at the time of approval by sending the Submission information from the Short Summary field in RMS-BLA in an email with the Subject line: "Lot Clearance" to the "CBER Lot Clearance" mailbox prior to beginning the approval process. Be sure to include all relevant lot numbers. **[RPM]**
6. Verify the appropriate review and signoff on the lot release protocols have been completed. **[PRB]**
7. Email the signed approval letter to "CBER Lot Clearance" mailbox on the day of approval. **[RPM]**
8. Generate and deliver notification of release as appropriate for launch lots. **[PRB and DMPQ Division Director]**

VIII. Appendix

A. NA

IX. References

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

1. R 900.01: Reviewer Considerations for CBER Product Testing Post-Licensure
2. R 900.02: Reviewer Considerations for Post-Market Product Assessment
3. R 900.03: Reviewer Considerations for CBER Product Testing In-Support of Licensing Action
4. R 900.04: Reviewer Considerations for Manufacturer's Lot Release Protocol Template
5. T 910.03: Testing In-Support Results Memo
6. Product Release Branch (PRB) Form 201: Sample Request Form (obtained from the PRB)
7. Lot Release System User Guide (found in the LRS)
8. Laboratory Quality System Policy Manual (found in the LQDB)

B. Web links to the references below can be found in the list following the History Section

1. SOPP 8401: Administrative Processing of Biologics License Application (BLA) http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073074.htm
2. SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073088.htm
3. FDA Staff Manual Guide 2350.1 Guidance for the Implementation of the Federal Managers' Financial Integrity Act (FMFIA) http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM257105.pdf
4. OMB revised Circular A-123, dated December 21, 2004 Management's Responsibility for Internal Control https://www.whitehouse.gov/omb/circulars_a123_rev

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Hollerbach	Christopher Joneckis, PhD	February 27, 2017	2	Revised procedures; removed information for supplements (to be included in new SOPP 8408.2). Technical revision to update to new required Font.
Jansen, Dixon	Robert A. Yetter, Ph.D.	February 18, 2011	1	