SOPP 8408.3: Lot Release Activities for Licensed Biological Products

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for the Center for Biologics Evaluation and Research (CBER) staff involved with the lot release program for licensed biological products.

II. Scope

A. This SOPP applies to CBER staff involved with the lot release program for the receipt, review, and testing of licensed products that are subject to lot release including licensed products that are submitted as surveillance lots (alternative to lot release).

B. This SOPP does not apply to products that are exempt from lot release or lots that are submitted in support of an application or supplement.

III. Background

A. The lot release process is part of the Food and Drug Administration's multi-part strategy that helps ensure licensed biological product safety by providing a real-

time system to monitor product quality. In accordance with 21 CFR 610.2(a), CBER has the authority to require the submission of samples and protocols for any licensed product for CBER review and confirmatory testing, i.e., lot release, when deemed necessary for the safety, purity, or potency of the product. Manufacturers are required by the terms of their license to submit information and data related to the lot in the form of a protocol and submit representative samples of the lot for confirmatory testing. CBER evaluates the information submitted and determines whether confirmatory testing is needed according to the approved testing plan for the product.

B. The approved license application describes what lot release testing the manufacturer performs and, through communication with CBER, it is determined what testing information should be included in their lot release protocol. If the product is subject to lot release, the manufacturer may not release the lot for distribution until the lot has been released by CBER.

C. Manufacturers may, sometime after approval of the original application, submit a supplement to request the product be moved from Lot Release and be put onto surveillance. If the supplement is approved, then a limited number of lots (protocols and/or samples) are submitted periodically to CBER, but a final release from CBER is not necessary prior to distribution of the product. See Appendix A, Federal Register notice 58 FR 38771 – 38773 (July 20, 1993), for more information on the requirements of information to be in the supplement.

IV. Definitions

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

B. 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.

C. 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.

D. Lot Release – Condition of licensure whereby the manufacturer is required to submit lot-specific protocols and possibly samples for review. **Note:** The manufacture may not distribute lots until the lot is released by CBER.

E. 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.

F. Lot Release Protocol (LRP) – 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.

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

H. Product Release Branch (PRB) – Official sample custodian for CBER and mailing address for samples and protocols.

I. Protocol Reviewer – Staff responsible for ensuring the accuracy of the information submitted on the lot release protocol.

J. Samples – Representative units of a product lot submitted by the applicant to the CBER Sample Custodian for CBER laboratories to conduct a review and/or specific control testing in support of lot releases, surveillances or licensing actions.

K. Surveillance Plan– Condition of licensure, usually conferred by the approval of a supplement to the Biologics License Application (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.

L. Testing laboratories – For the purposes of this SOPP, any CBER laboratory that tests regulated product for Lot Release or Surveillance.

V. Policy

A. It is CBER policy that lots submitted for release should be released within 30 business days of receipt of a complete lot release package. A complete package includes both a protocol and samples (when samples are required). All protocol

reviewers, as well as those involved with the testing of samples, should make every effort to complete their part of the review and/or testing as soon as possible. Delays (of greater than 7 days) should be conveyed to the Product Release Branch (PRB) staff so that attempts can be made to address issues in order to meet the 30 day release timeframe.

B. Often the samples are submitted well before the lot release protocol to allow for CBER testing. Testing laboratories are to begin, when possible, to request samples from PRB and complete the testing according to the testing plan as soon as the sample is available and not wait for the corresponding protocol to be submitted.

C. Under certain circumstances (short supply) the manufacturer may request expedited release of a product lot. These requests should be made through the CBER Product Shortage Coordinator (refer to *SOPP 8506: Management of Shortages of CBER Regulated Products*).

VI. Responsibilities

A. PRB Staff

1. Has overall responsibility for product samples (receipt, storage and disposal) and protocols (receipt, processing, tracking, and sending completed lot release packages to the Document Control Center (DCC) for archiving);

2. Communicates with manufactures for corrections to protocols or requests for additional samples for testing;

3. Coordinates review of lot release protocols and testing (when performed); including tracking progress of the release of product lots, ensuring sign off by appropriate staff, completion of testing (when required), and resolution of any issues raised during the review; and

4. Ensures the lot release notification is prepared and sent to the manufacturer within CBER's specified timeframe.

B. Testing Laboratories – responsible for testing samples in accordance with the Laboratory Quality Product Testing Plan and with sufficient time to ensure testing is complete within CBER's review timeframe and notifying PRB if there are delays in testing.

C. Protocol Reviewers – responsible for determining whether the information in the protocol is complete and an accurate reflection of the currently approved tests and specifications.

D. Document Control Center – responsible for receiving and archiving documents, including lot release protocols, from regulated companies and from within CBER.

VII. Procedures

A. Samples

1. Receive, enter information into LRS and place samples in PRB cold storage units under the appropriate storage temperatures. **[PRB]**

2. Notify testing laboratories that samples are available for testing. **[PRB]**

3. Determine what testing needs to be performed in accordance with the Laboratory Quality Product Testing Plan. **[Testing Laboratories]**

4. Request samples from PRB as needed for testing. **[Testing Laboratories]**

5. Perform required testing with sufficient time to ensure testing is complete within CBER's review timeframe and dispose of remaining unused samples after testing is complete. **[Testing Laboratories]**

6. Record test results according to laboratory SOPPs in the Laboratory Quality System, and note completion of testing in the LRS. **[Testing Laboratories]**

7. Dispose of unused samples remaining in PRB cold units per sample retention policies. **[PRB]**

B. Protocol

1. Perform the initial receipt of protocols (paper or electronic) and ensure the information is correct. **[PRB]**

- **a.** Contact the manufacturer and request corrections as needed. **[PRB]**

2. Assemble paper protocols and route to the appropriate reviewers as designated on the attached route slip; or ensure electronic lot release protocols are available for staff review. **[PRB]**

3. Examine the information and test data in the protocol that corresponds to the reviewer's area of responsibility upon receipt of a lot release protocol. **[Protocol Reviewer]**

4. Determine if the information is sufficient or whether additional information is necessary. **[Protocol Reviewer]**

5. Contact PRB within seven days of receipt of protocol if additional information or corrections are necessary. **[Protocol Reviewer]**
   a. Contact the manufacturer and request corrections as needed and provide corrections to Protocol Reviewer as received. **[PRB]**

6. Sign-off on the review in the LRS (for both electronic and paper submissions) after the review and/or testing is complete. Note: For paper submissions, also complete sign-off on the route slip and send to the next reviewer on the list. **[Protocol Reviewer]**

7. For paper only submissions, return the paper protocol to PRB when all protocol reviews have been completed. **[Protocol Reviewer]**

C. When all testing and protocol reviews have been completed:

1. Review completed lot release package, ensuring accuracy and sign-off are completed by testing laboratories, as applicable, and protocol reviewers. **[PRB]**

2. Prepare lot release notice which is reviewed and signed by the lot release signature authority in CBER. **[PRB]**

3. Send notification to the manufacturer via fax and follow-up by mail with a paper copy of the release. **[PRB]**

4. File completed lot release packages (protocol and release letter) in PRB. After 60 days, compare to the release list prepared by date and send the completed lot release packages to DCC. **[PRB]**

VIII. Appendix

A. Federal Register notice 58 FR 38771 – 38773 (July 20, 1993)

IX. References

A. References below may be found on the Internet:

1. 21 CFR 610.2
2. SOPP 8408.1: Development of Laboratory Quality Product Testing Plans and Release of Lots as Part of the BLA Approval Process
3. SOPP 8506: Management of Shortages of CBER Regulated Products

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Monser	N/A (reviewed by Job Aid Coordinator)	September 25, 2019	2	NO CONTENT CHANGE: Technical Update to update hyperlinks and to current font/format
Eltermann	Chris Joneckis, PhD	June 17, 2018	1	Original Version