United States Department of Agriculture
Center for Veterinary Biologics
Standard Operating Policy/Procedure

Reference and Reagent Review and Release

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1. Purpose

The purpose of this document is to describe the reference and reagent review and release procedure used by the Center for Veterinary Biologics (CVB).

2. Scope

This document is intended to establish a process for reviewing and managing records for the release of CVB reagents and references (see **Section 3**) that are critical components in biological testing. This release procedure is for reagents and references qualified by the CVB, either manufactured by the CVB or other entities, for distribution to biologics firms or others outside of the CVB. Limited-Use Biologics are excluded from the scope of this document. Also, this process is not intended to apply to the references or reagents produced by biologics firms for their own master seed or release tests that do not require CVB references or reagents.

3. Definitions

3.1 Critical Component: A biologic reagent or reference that provides integral properties required by a test system to directly support a result or test validity.

3.2 CVB Reagent and Reference Catalog: A current list of reagents and references supplied by the CVB that are supported by a Reagent/Reference Folder, excluding Limited-Use Biologics.

3.3 Draft Production Protocol: A specific type of draft document that defines a production protocol for a reference/reagent that is in the developmental stage. When a reference/reagent is produced using a draft production protocol, the reference/reagent is considered to be nonstandard and a complete copy of the draft production protocol must be included in the reference/reagent folder. Additionally, this draft copy must be signed by the Section Leader (or their designee), both to provide accountability for how this particular reference/reagent was produced and also to document management acknowledgment of the production of a nonstandard reference/reagent (see **QMSOP0001**, *Center for Veterinary Biologics Quality Management System Documents*).

3.4 Point-of-Use Biologic: A biological agent prepared at the CVB intended for internal use (i.e., master seed virus). A *point-of-use biologic* is not required to undergo the review and release parameters described in this document. Manufacturing and test records are maintained by the CVB Laboratory Section responsible for producing this biological entity. Under special circumstances, CVB may supply a *point-of-use biologic* to firms or other entities. The Section Leader or designee will communicate with the intended recipient via letter the intended use of the biological. This information is essential to ensure that the recipient understands this agent has not been through the reference and reagent review and release process. A **CVBFRM3101**, *Point of Use*

Biologic Sign-off Form, is completed and kept in the reagent/agent file. Other relevant information such as a reagent data sheet may accompany the shipment.

3.5 Production Protocol: The term used to designate a specialized SOP describing a specific way to carry out a production process used in the CVB Laboratory.

3.6 Reference/Reagent Folder: A single, well-organized file that includes all pertinent records associated with the reagent or reference.

3.7 Standard Test Reagent (Reagent): This is a serum, antitoxin, fluorescent antibody conjugate, toxin, virus, bacterial culture, or antigen to be used in test systems but not for direct comparison with serials of biological products under test.

3.8 Standard Reference Preparation (Reference): This is a serum, virus, bacterial culture, cell, or antigen to be used in test systems for direct comparison with serials of biological products under test.

3.9 Section: In this document, "Section" refers to the Section within the CVB preparing the reagent or reference.

4. Policies and Objectives

The reference and reagent review and release procedure shall meet any applicable standards within title 9, *Code of Federal Regulations* (9 CFR), part 113, and of the quality system of the Laboratory. This procedure is intended to provide a scientifically valid and consistent process for the release of reagents and references for use. In addition, this reference and reagent review and release procedure is designed to facilitate the continuous improvement of CVB reference materials and reagents supplied to the biologics industry and others.

5. Roles and Responsibilities

5.1 Staff: Members of the CVB staff are responsible for following all procedures associated with reagent and reference preparation review and release. The staff is also responsible for following currently accepted good manufacturing and laboratory practices in the production and evaluation of reagents and reference preparations.

5.2 Management: CVB management is responsible for final review and approval of all information contained in the Reagent Folder and for providing resources and training required by staff to produce quality references and reagents.

6. Processes

6.1 In the case of a CVB-produced reference or reagent, all documentation regarding the production and testing of the reagent or reference is organized in a Reagent/Reference Folder. The cover is labeled with the product name, lot number, and responsible laboratory section. The Reference/Reagent Folder includes the following, in order: Table of Contents; **CVBFRM0009**, *Reagent Production Sign-Off Form;* **CVBFRM0008**, *CVB Reference and Reagent Test Report*; Reagent Data Sheet; Production or Draft Protocol; certificate of source for ingredients of animal origin; production records; in-process testing; fill and label records; final product testing; and notes. An example of a Reference/Reagent Folder template is **CVBFRM3001**, *Documentation for Reference and Reagent Folder*.

6.2 In the case of third-party acquired references or reagents, the Section Leader or designee shall ensure copies of the production records, negotiated contract, or any other paperwork associated with the reagent or reference is included in the Reference/Reagent Folder.

6.3 Following completion of the reference or reagent, the manufacturing Section shall review the contents of the Reference/Reagent Folder and sign **CVBFRM0009**. Their dated signature indicates that 1) the records were found to be legible and complete, and 2) all of the required information and testing is contained in the Reference/Reagent Folder.

Note: The manufacturing Section review shall not be completed by the primary individual who produced the reagent.

6.4 Following the manufacturing Section review, the Section Leader or their designee shall review the contents of the Reference/Reagent Folder and sign **CVBFRM0009**. Their dated signature indicates that 1) the records were found to be legible and complete, and 2) all of the required information and testing is contained in the Reference/Reagent Folder.

6.5 Following review by the manufacturing Section Leader or their designee, submit the Reference/Reagent Folder to the Lead Biologics Compliance Assistant (BCA) for review and release. The Lead BCA stamps the documents as received and forwards to the assigned Biologics Specialist. The Biologics Specialist reviews the information on **CVBFRM0008** and compares it to the information on the Reagent Data Sheet and the Production Protocol. If the documentation is correct, the Biologics Specialist initials and dates the Reagent Data Sheet, signs and checks the APHIS disposition box on **CVBFRM0008**, signs **CVBFRM0009**, and returns the folder to the Lead BCA.

6.6 The Lead BCA stamps the signed documents and makes sure the appropriate disposition has been selected by the Biologics Specialist.

6.7 If the reference or reagent is signed off as Satisfactory for release by Inspection and Compliance (IC), the Lead BCA forwards the documents to the CVB Quality Management System (QMS) Program Assistant. The QMS Program Assistant scans the Reagent Data Sheet and **CVBFRM0008** and uploads the documents to the CVB QMS SharePoint site, [redacted].

6.8 The Reference/Reagent Folder is returned to the originating Section by the QMS Program Assistant. The product is added to the Section inventory and is available for use and distribution.

6.9 If the reference or reagent does not satisfy the requirements set forth in the Production Protocol, the product will be considered Unsatisfactory for the intended use.

6.10 Documentation of the disposition of unsatisfactory product, along with the **CVBFRM0008**, is to be filed in the Reference/Reagent Folder.

7. Records

7.1 Production and test records should be initialed (or signed) and dated by the person performing the work.

7.2 Each page of all generated documentation relevant to the production, testing, review, and release of a reference or reagent shall be identified with the reference/reagent unique identification number.

7.3 The Reference/Reagent Folder shall be filed in the CVB Laboratory Section and will be maintained indefinitely.

7.4 Fill out **PIMSFRM1108**, *Document Publication Form*, to have the reagent data sheet posted on the CVB Website.

7.5 **Reagent Catalog:** For reagents that will be shipped to manufacturers, alert Nancy Clough of the Policy, Evaluation, and Licensing (PEL) Virology Section to enter the reagent into the Reagent Catalogue. Provide the reagent name, lot number, fill volume, and that the reagent is available for shipping. If the new reagent is replacing a current reagent, also notify her to take the old lot number off the reagent catalog.

7.6 If additional testing is completed on a released reagent (i.e., for reagents that have expiration dates that require testing to extend the expiration date, or when a reagent has been shared with firms for concurrent testing prior to completion of testing at the CVB) an updated Reagent Data Sheet needs to be approved and posted.

7.7 All correspondence following release of the reagent, including customer feedback, will be saved to the CVB Lab drive under “Reagent Correspondence.”

Documents will be saved in a corresponding file referencing agent name and specific lot number (i.e., Clostridium septicum toxin IRP 628).

8. Customer Feedback

8.1 The CVB Mail Box address, CVB@aphis.usda.gov, is provided on the Reagent Data Sheet for any feedback from the customer regarding the reagent. These emails are received by the IC Program Support Assistant and forwarded to individuals in the email group, APHIS-VS STAS CVB Reagent Requests, for appropriate action.

8.2 Any correspondence received by CVB personnel regarding a supplied reagent, including but not limited to emails, phone logs, mail logs, etc., should be sent directly to the email group, APHIS-VS STAS CVB Reagent Requests, for appropriate action.

8.3. The laboratory section that produced the reagent is responsible for all appropriate follow-up to the feedback and for maintaining records documenting any correspondence or action taken.

8.4 All emailed documents will be reviewed and saved by the manufacturing section to the CVB Lab drive under "Reagent Correspondence." Documents will be saved in a corresponding file referencing agent name and specific lot number (i.e., Clostridium septicum toxin IRP 628).

9. Summary of Revisions

Version .09

- **3.4:** In definitions, changed Limited-Use Biologics to Point-of-Use Biologic and definition updated to reflect internal use terminology.

Version .08

- **7.5:** Added instructions for the Reagent Catalog.
- **7.6:** Added instructions for updating Reagent Data Sheets
- **7.7, 8.3, and 8.4:** Added information on Section Responsibility for managing customer concerns.
- **8.1 and 8.2:** Added information on routing of customer feedback received via the CVB Mail Box.

- Other minor clarifications.

Version .07

- **6.5:** Clarified steps performed by Lead BCA and changed Quality Management Biologics Specialist to assigned Biologics Specialist due to pending reorganization.

- **6.6:** Moved reference to returning folder to originating section from 6.6 to 6.8 - folder will not be returned until processed.

- **6.7:** Changed procedure – QMS will scan documents prior to returning to the originating section. Removed requirement to scan and upload CVBFRM0009 – the form is not required for tracking of approval.

- **6.8:** The folder will be returned to the originating section after documents are scanned and up loaded. The originating section will not be responsible for scanning and emailing the documents.

Version .06

- **3:** Definitions for Draft Production Protocol was updated

- Document was updated for consistency

Version .05

- The Contact information has been updated.

- This document has undergone a complete revision after extensive review by the entire Center.

Version .04

- **3:** Definitions for Draft Production Protocol and Production Protocol have been added.

- **3/6.5:** Clarification has been added to the reference "all pertinent records of production".

- **6:** Provision that a copy of the Production Protocol need not be provided to the QM Specialist if the protocol is available on the CVB Quality Management SharePoint site, and that any protocols or 3rd party contract provided to IC for review are CBI'd and not filed has been added. Provision for 2 copies of the CVBFRM0009 allowing one copy to be retained by the ABRM Section and one to be sent to the originating

Section has been added. "IC-OAA" is replaced with "Lead BCA", and the return of all copies to ABRM for further distribution has been added to reflect the current pro**c**ess.

- **6.11:** Disposition of the 3 CVBFRM0008s has been clarified.

Version .03

- **3:** The definition of Reagent Folder has been updated with further clarification of what is needed.
- **5.2:** The requirements for Management have been updated with further clarification of what is needed.

- **6:** The processes for reference and reagent review and release have been updated with further clarification of what is needed.

- The document number has been changed to CVBSOP3001 to reflect new Unit delineations.

- The section on "Standards and Normative References" has been removed.

- The section on "Forms and Worksheets" has been removed as these are referenced throughout the document.

- The section on "Monitoring Process for Effectiveness" has been removed as all CVB Quality Management System documents and their processes are open to audit.

- The "Appendix" has been removed and made into a self-standing form, CVBFRM3001.

Version .02

- PELSOP0001.02 is a revision superseding CVBPELSOP0001.01.
- CVBPELSOP0001 was changed to PELSOP0001 to reflect the new, streamlined Unit Abbreviations.
- Section and Reagent Folder definitions were added to the Definitions Section.
- ISO/IEC 17025 reference was removed from the Standards and Normative References Section as this SOP deals with reference and reagent production processes and not testing competency.
- CVBQASOP0001, CVB Quality Assurance Program Documents, was added to the Standards and Normative References Section.
- The retention date for Records (now Reagent Folders) was changed from 7 years to 10 years to be in compliance with the APHIS Records Management Handbook.

- Audits "as required by the CVB Quality Assurance Program" was added to the Monitoring Process for Effectiveness Section.
- Appendix 1, CVB Reference and Reagent Test Report, was removed as that information is now captured on CVBQAFRM0008, current version.
- CVBFRM0001.01 and CVBPELFRM0002.01 were removed from the end of this SOP, as they were not an official part of the document. Both of these forms have been retired.
- General clarification of duties and processes and adjustments to formatting have been made throughout this SOP. Refer to the "Track Changes" copy for specifics.