Frederick National Laboratory for Cancer Research, Frederick, MD

BDP

Biopharmaceutical Development Program

Standard Operating Procedure

Title: BOP Reference Material Management

SOP Number: 22716

Revision Number: 02

Supersedes: Revision 01

Effective Date: JUN 22 2017

Originator/Date: [redacted]

Approval/Date:

Approval/Date:

Table of Contents

1.0 Purpose

This procedure describes the management of reference materials produced at the Biopharmaceutical Development Program (BOP}, Leidos Biomedical Research, Inc.

2.0 Scope

This procedure applies to Biopharmaceutical Development Program/Leidos Biomedical Research, Inc., personnel who prepare, test, inventory, or store reference material. This procedure does not apply to pH, conductivity, and molecular standards.

3.0 Definitions

3.1 Reference Standard: A material or substance whose properties are sufficiently characterized to be used for the assessment of test samples obtained from a lot of material manufactured by or for the BOP. This standard can be: (1) obtained from an officially recognized source, (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted]

3.2 Compendial Reference Standards, such as those purchased from the United States Pharmacopoeia (USP) or British Pharmacopoeia (BP), are considered "official" and do not need to be characterized prior to use. However, when available, standards must have Certificates of Analysis (COA) from the vendor and results obtained from the COA must be comparable to the previous COA.

3.3 Non-compendial (Commercial) Reference Standards must have a COA from the vendor, and be within the shelf life. Commercial Reference Standards are to be tested by the receiving laboratory prior to use. If no COA is available then full characterization will be conducted by PA\QC.

3.4 "In-House" Reference Standards can be prepared by further purification, if necessary, from existing production material.

3.5 Primary Reference Standard: A substance that has been shown by an extensive set of analytical tests to be authentic material of high purity.

3.6 Secondary Reference Standard: When the initial supply of the primary standard is low, a second primary standard will be prepared. A material or substance whose properties are characterized by comparison to the primary reference standard. Once characterized, the secondary reference standard is used to assess test sample material manufactured using the same process.

4.0 Authority and Responsibility

4.1 The Director, Biopharmaceutical Process Analytics (PA)\Quality Control (QC) has the authority to define this procedure.

4.2 Development, Manufacturing, or Laboratory personnel are responsible for the preparation/documentation of the reference standard and coordination of testing submissions.

4.3 PA\QC personnel are responsible for testing the reference material, approving, and/or creating a COA, and storing the reference material.

4.4 PA\QC is responsible for reviewing the data and documentation of the results of this procedure.

4.5 The Project Scientist or designee is responsible for ensuring the creation of the Primary Standard by either identifying or providing the reference standard(s) for use in PA\QC assays.

4.6 BQA is responsible for quality oversight of this procedure.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

5.0 Procedures and Primary and Secondary Reference Standards

5.1 Preparation of Reference Materials

5.1.1 When possible and appropriate, the reference material is manufactured in the same manner as the bulk drug substance. The reference standard can be apportioned from a pilot scale purified bulk lot produced during the product development stage, or from tox or GMP lots.

5.1.2 Reference material will be aseptically aliquoted in a Laminar Flow hood or other classified area.

5.1.3 Provide documentation of the characterization, storage conditions, and formulation supportive of reference material(s) stability to BQA. The preparation of reference materials can be documented in either a laboratory notebook or using an approved or draft master production record.

5.1.4 Unless obtained from external sources, the reference material is labeled according to ***SOP 21403 Origination, Modification, and Control of Labels*.**

5.2 Testing of Reference Materials

5.2.1 The reference material is characterized for concentration, identity, and purity at a minimum and, where appropriate, activity or potency testing should be performed. A draft Master Specification may be used that describes the testing proposed to establish the identity, concentration, purity, and other quality characteristics of the reference material.

5.2.2 Unless the reference material is provided with a Certificate of Analysis (COA) from the manufacturer, the reference material is tested and documented on Biopharmaceutical Quality Control Test Request Form 22002-01, as per ***SOP 22002 Request for Quality Control Testing*.**

5.2.3 A COA is prepared by PA\QC summarizing the tests performed, the test methods, the specifications if available, and the results.

5.2.4 Manufacturer's COAs for reference materials will be archived by BDP QA and a scan and/or hard-copy will be retained by the BDP Reference Material Program.

5.2.5 The suitability of each batch of secondary reference standard must be determined prior to first use by comparing against a primary reference standard in a bridging study comprised of tests for the key quality attributes of the product.

5.2.6 Reference Materials may be monitored for real-time stability following an approved stability protocol. Otherwise, reference materials are periodically requalified / retested when tested against a test sample. Any observation of reference degradation would be treated as an OOS and handled through ***SOP 22004 Managing Out-of-Specification Test Results or Unexpected Test Results***.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

5.2.7 In addition to biological assays (potency), stability-indicating physicochemical assays are performed on reference standards along with the test samples in any stability protocol. Any degradation of the reference standard that was not evident in the potency assay would be indicated by the appearance of degradation products in the physicochemical assays. An example of this is SEC-HPLC where the system suitability is determined by independent calibration standards. Any product or reference standard degradation by aggregation would be evident in the SEC chromatogram. The reference material or standard is expected to meet the same fixed physicochemical criteria and specifications as the test sample. Reference material that falls out of these established ranges would either lead to an invalid assay or an OOS – either of which would trigger a review or formal investigation of the standard itself.

5.3 Control, Inventory, and Storage of Reference Materials

5.3.1 Reference materials are stored at either ≤ -70°C, -10°C to -30°C, or 2° - 8°C as appropriate for the material being stored. The reference material is stored in controlled freezers and refrigerators located in PA\QC laboratories.

5.3.2 Reference materials are deposited in the PA\QC freezers and refrigerators through the PA\QC Accessioning Office per ***SOP 22006 Accession Log Data Entry Procedure for QC Bound Logbook and QC Access Database.*** A Sample Input sheet is completed by the requestor and PA/QC Accessioning Office personnel that includes lot number, storage temperature, sample description, date received, quantity received, and freezer/rack/box location. The information from the Sample Input sheet is entered into a Freezer Inventory Database system for Reference Standards and the hard copy is stored in a binder by PA\QC Accessioning Office personnel.

5.3.3 Reference materials removed from inventory for non-BDP use are documented per ***SOP 22008 Sample Withdrawal from the Quality Control Inventory*** using the PA\QC Sample Withdrawal Form 22008-01. Withdraw of reference materials from controlled PA\QC inventory for any purpose is captured in Form 20303-01 and in the Freezer Inventory Database (FreezerWorks). The Freezer Inventory Database system for reference standards is updated to reflect the withdrawal, and the paper copy (Form 20303-01) is stored in a binder by PA\QC Accessioning Office personnel.

6.0 References and Related Documents

References listed below can be obtained by visiting the Biopharmaceutical Quality Assurance Regulatory Affairs Group, or the FDA website (www.fda.gov).

6.1 21 CFR 211.160 – Laboratory Controls General Requirements.

6.2 International Conference on Harmonization (ICH) Harmonized Tripartite Guideline Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

6.3 FDA Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

6.4 FDA Guidance for Industry: For the Submission of Chemistry, Manufacturing, and Control Information for Synthetic Peptide Substances.

6.5 **SOP 21403** *Origination, Modification, and Control of Labels*

6.6 **SOP 22002** *Request for Quality Control Testing.*

6.7 **SOP 22006** *Accession Log Data Entry Procedure for QC Bound Logbook and QC Access Database*

6.8 **SOP 22008** *Sample Withdrawal from the Quality Control*

6.9 **SOP 22004** *Managing Out-of-Specification Test Results or Unexpected Test Results*

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].