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1.0 Purpose

This SOP outlines the procedure for scheduling, performing, and reporting the results of Current Good Manufacturing Practice (CGMP) compliance audits of the Biopharmaceutical Development Program (BOP) operations, procedures , and areas.

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

2.0 Scope

Biopharmaceutical Quality Assurance (BQA) conducts internal audits to ensure that the areas, processes, systems, and procedures comply with CGMP regulations (21 CFR 211 and 21 CFR 610) as appropriate for the manufacturing and testing of biopharmaceutical Phase I/II clinical products.

Audits are performed on areas involved in the production and testing of products as well as those areas that have a supportive function [Materials Management, Inventory Control (MMIC), Process Analytics/Quality Control (PA/QC), Sterilization, etc.]. Audits may also be conducted on a specific process (i.e., purification) and on systems (i.e., environmental monitoring or employee training).

BQA conducts both scheduled and unscheduled audits. Audits may involve a single auditor or group of auditors who will audit a predefined area by touring the facility, observing employee activities, and reviewing records/documentation.

3.0 Authority and Responsibility

3.1 The Director, BQA has the authority to define and update this procedure.

3.2 The BQA Manager is responsible for the following:

3.2.1 Audit scheduling.

3.2.2 Conducting audits and completing audit reports.

3.2.3 Reporting observations and findings to the audited Area Manager.

3.2.4 Maintaining the CGMP Audit Spreadsheet.

3.2.5 Follow-up and closeout of identified corrective actions.

3.3 The BQA Manager is responsible for alerting BDP management to observations that could possibly impact product safety, identity, strength, quality, or purity.

3.4 BDP Management is responsible for reviewing the audit report and implementing corrective and preventative actions (CAPA), documenting CAPA activities, and updating BQA as to CAPA and related progress.

4.0 Audit Schedule

4.1 Area audits are scheduled on an annual basis. Refer to Section 13.1 for audit focus areas.

4.2 System audits are scheduled as directed by the BQA Director or BQA Manager.

4.3 An audit schedule is prepared by the BQA Auditing department outlining the areas/systems to be audited, when the audit is to be conducted, and the auditor(s) assigned to conduct the audit.

4.4 Walk-through audits may be conducted on a random basis. The frequency of walk-through audits may be increased/decreased as directed by the BQA Manager.

4.5 Product and For Cause audits are conducted as directed by BQA or BDP Management.

5.0 Audit Procedure (Area, Process, System, Product, For Cause)

5.1 Scheduled audits are conducted in cooperation with the area's management. Contact the area's Director or Manager to schedule a time to conduct the audit.

5.2 Prior to the audit, review relevant documentation (organization chart, facility diagram, process flow diagrams, Standard Operating Procedures (SOP) index and SOPs, previous

internal audit reports, and third-party audit reports) to become familiar with personnel, layout of the facility, operations conducted, SOPs used by the department, previous observations, and CAPA commitments.

5.3 Prior to entering any work area, gown as appropriate for entering those areas.

5.4 If possible, conduct tours of the area when operations are in progress to observe personnel and procedures under dynamic work conditions. Compare personnel activities and completed documentation to SOP requirements. Auditors may develop a checklist of items to be verified during the audit. Auditors must be cognizant of their potential impact on manufacturing and testing operations. Auditors shall be considerate and not interfere with operations underway.

5.5 During the audit, record areas and operations audited, personnel audited, and dates of the audit. Record any potential deviations from CGMPs, SOP requirements, or any other observed conditions warranting follow up with management. If the Area Supervisor or Manager accompanies the audit, review any observation with him/her to ensure issues are understood by both the auditor and management.

5.6 If any observation is deemed by the auditor to impact the safety, identity, strength, quality, or purity of a product, bring these observations in writing to the immediate attention of BQA and BDP management.

5.7 Document the performance of the audit in the Internal CGMP Audit Spreadsheet located in BQA. Note the date of the audit, the area audited, auditor names(s), and audit close-out date. Regulatory agencies may review the audit log, upon request.

6.0 Audit Report

6.1 At the conclusion of the audit (except as needed for walk-through audits), a spreadsheet will be prepared summarizing the audit observation/findings.

6.1.1 Identify the area audited, date(s) of audit, auditor(s) and any other relevant information about the audit.

6.1.2 List observations requiring corrective action. Provide a description of the observation supported with objective evidence (if available).

6.1.3 Describe any long-term corrective and preventative actions for the area that may have remained from the previous area audit and indicate the current status of those items.

6.2 Audit observations that reveal potential negative product impact will initiate quality event investigations, see ***SOP 21008 - BDP Material Review Board***.

6.3 Regulatory agencies are <u>not</u> permitted to review internal audit reports and documentation.

6.3.1 Regulatory agencies are permitted to view the Internal CGMP Audit Log to verify that internal audits were performed.

7.0 Audit Response

7.1 The Manager or Supervisor of the area audited will review the audit observations, develop a CAPA plan with target dates for completion, and institute CAPA actions.

7.2 The Manager/Supervisor will respond in writing to the audit report with the details of any CAPA taken and/or planned. The response should be submitted to the BQA Auditor within 30 days (target) of receipt of the audit report.

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

7.3 BQA will review the written responses and determine the acceptability of any CAPA taken and planned. Any unacceptable issues will be reviewed with the area management for resolution.

8.0 Audit Follow-Up and Closeout

8.1 BQA will verify corrective actions. A follow-up audit may be necessary.

8.2 When short-term and any potential product impact corrective actions have been implemented and have been verified as complete, the audit will be considered closed.

8.3 Long-term corrective and preventative actions are noted in the closeout letter for follow-up during the next audit or at an interval defined by the BQA Audit Manager.

8.4 Include the results of any follow-up audits in the audit file with the original report.

8.5 Record the date of closeout in the BQA Audit Spreadsheet.

9.0 Walk-Through Audit Procedure

9.1 Following required gowning practices, tour the selected operational areas of the BDP (refer to Section 13.1 for areas).

9.2 Should operations be dynamic in the area, observe personnel practices in these areas.

9.3 Observe the condition of the building and equipment being used in the area.

9.4 Review a random selection of documentation (logbooks, lab notebooks, cleaning logs, etc.) and review the degree of completeness, accuracy and good documentation practices.

9.5 Discuss observations with relevant personnel. Report significant concerns to the area management.

9.6 Should conditions warrant further actions, the walk-through audit may be converted into or followed up with an audit as described under Section 5.0 upon review with the BQA Manager.

9.7 Record the date of the walk-through audit, the area or operation observed, and the name of the auditor in the Internal Audit Log Spreadsheet.

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

10.0 BQA Audit Log

10.1 For the internal audits conducted (area, product, process, system, and walk-through), complete an entry in the Internal CGMP Audit Log.

10.2 Complete the log entry by recording the following.

- Audit Date
- Areas Audited
- Audit Type
- Audit Phase
- Purpose or Activity
- Project Number/SOP Number
- Location
- Lead Auditor
- Status
- Date Audit Completed

11.0 Audit Schedule

11.1 The Audit Schedule is updated during the audit process with the following audit status assigned.

- Audit to be scheduled (TBS)
- Audit scheduled
- Report pending
- Response pending
- Audit closed and date closed.

12.0 Documentation

12.1 Final audit and any supportive records or documentation shall be kept on file (electronic and/or paper).

12.2 Paper audit records may be stored off site at a document storage facility.

13.0 Definitions

13.1 **Area Audit –** An audit of a production, testing (PA/QC), or support area in which a review of operations, SOPs, and other documentation, facilities, cleaning, preventive maintenance, employee training, etc., are examined in a comprehensive manner. Area audits are usually pre-scheduled. These areas include, but are not limited to, the following.

13.1.1 MMIC (Shipping and Receiving).

13.1.2 Manufacturing Areas

13.1.3 Process Analytic/Quality Control Laboratories.

13.1.4 Support Areas.

13.2 **Audit Team –** The group of individuals who will perform the audit. The BQA Audit Manager (or designee) will lead the team. Other team members may include:

13.2.1 Persons from "peer" BDP departments.

13.2.2 NCI personnel.

13.2.3 Consultant auditors.

13.2.4 Others as is appropriate to the audit to be conducted.

13.3 **Corrective and Preventative Actions (CAPA) –**Corrective actions include steps taken to rectify issues of immediate concern. Preventative actions address longer-term issues, usually related to root cause determination and remediation.

13.4 **For Cause Audit –** A directed audit to assess a product, area, process, or system that has shown non-compliance, has been involved in a complaint, or needs additional follow-up to verify continued compliance or to verify implementation of corrective action. For cause audits may be scheduled or unscheduled.

13.5 **Process Audit –** An audit of a process to confirm that the process is being conducted according to approved written procedures and specifications.

13.6 **Product Audit –** An audit of the manufacturing and/or testing of a specific product. This includes reviewing raw materials, batch production records, product testing, packaging, labeling, and shipping activities. Product audits are usually pre-scheduled. Product audits may be the result of a product complaint.

13.7 **System Audit –** An audit of a major system and its control activities within an area or across multiple areas. System audits include, but are not limited, to the following.

13.7.1 Personnel Training.

13.7.2 Employee Gowning.

13.7.3 Document Control.

13.7.4 Environmental Control.

13.7.5 Equipment Calibration Control.

13.7.6 Cleaning/Sanitization.

13.7.7 Raw Material Control.

13.8 **Walk-Throughs –** An informal walk through of an area designed to assess the compliance status at a specific moment in time. Walk-throughs provide a BQA presence to give other personnel an opportunity to ask compliance-related questions and discuss ideas and issues in an informal setting. These are short duration audits (usually 10-15 minutes) and allow the auditor to tour several operational areas in a day. Significant non-compliant observations are brought to the attention of the area management using a written memo from BQA outlining the non-compliance and requesting corrective action. Minor observations are discussed with relevant personnel during the walk-through. These audits allow for a snapshot type check on the compliance level of any given area. Walk-throughs are usually unscheduled.

14.0 References and Related Documents

14.1 **SOP 21008** *BDP Material Review Board*

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