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1.0 Purpose

This procedure describes the Biopharmaceutical Development Program's (BDP) policy for management of audits at the NCI/Leidos Biomedical Research, Inc., (LBR)/BDP facilities by sponsor auditors or the sponsor's third-party audit contractors.

2.0 Scope

This procedure applies to the sponsor's auditors and NCI/LBR/BDP personnel who interface with sponsor auditors or third-party auditors during inspections/audits of the BDP. This procedure does not apply to audits of the BDP conducted by or at the request of the National Cancer Institute, Biological Resources Branch personnel.

3.0 Policy

It is BDP's policy to encourage sponsor audits of the NCI/LBR/BDP premises, equipment, processes, facility, and compliance to CGMP regulations as are applicable for a Phase I/II investigational use clinical product manufacturer.

Whenever possible, audits will be conducted prior to the signing or approval of any manufacturing contracts between the sponsor and the BDP. This will allow the resolution of areas of concern before BDP is contracted to perform the service.

It is BDP's policy to restrict access to certain Manufacturing and or Quality Control areas when an audit of those areas would be disruptive to the activities being conducted.

Sponsor auditors must be able to conduct the audit with objectivity and be free of conflicts of interest. Therefore, previous employees of the BDP may not audit the BDP. The BDP maintains the right to refuse access to sponsor auditors if conflicts of interest may be an issue.

For general oversight of CGMP compliance, each of the various subject areas for GMP Compliance may be audited only once per year by the same sponsor regardless of the number of projects performed for the sponsor.

4.0 Introduction

The BDP cooperatively works with various sponsors in the biopharmaceutical development process to produce Phase I and II clinical products. The development of a productive working relationship between the BDP and its sponsors is an important factor in the technological success of projects and the efficient use of resources.

Auditing serves a valuable purpose for both the auditing and audited organizations. A well-executed audit allows sponsors to become knowledgeable about (and comment on) BDP systems, processes, and capabilities. It allows BDP to become more knowledgeable about sponsor requirements, expectations, and needs. Ongoing improvement may be achieved as sponsors provide suggestions and challenge BDP systems and as the BDP adjusts to meet changing industry practices. Ultimately, audits enhance the communication between partners (or potential partners) in the biopharmaceutical development process.

While auditing can be a valuable tool, it is resource intensive for both parties. This SOP has been designed to optimize the audit process, to provide for the efficient use of resources, and to discourage practices that interfere with the mission of the BDP.

5.0 Authority and Responsibility

5.1 The Director, Regulatory Compliance, Biopharmaceutical Quality Assurance (BQA), Biopharmaceutical Development Program (BDP) has the authority and responsibility for implementation of this procedure, which includes:

5.1.1 Authorizing the proposed audit agenda and audit scope (and any changes to the audit agenda or scope after the audit has started).

5.1.2 Providing oversight for agreed upon corrective and/or preventive actions.

5.1.3 Alerting BDP and BRB management of serious audit findings or circumstances that could impact the success of the audited project(s) and/or regulatory compliance.

5.2 The BQA Audit Manager is responsible for:

5.2.1 Hosting the audit.

5.2.2 Receiving the audit agenda from the sponsor.

5.2.3 Arranging for BDP personnel to be present as needed.

5.2.4 Scheduling a meeting area for the audit dates.

5.2.5 Providing a BQA escort for the auditors.

5.2.6 Assisting BDP personnel in the development and modification of corrective or preventive actions in response to sponsor audit observations.

5.2.7 Compiling internal responses to audit observations and providing a written response to the sponsor.

5.3 BDP personnel are responsible for assisting with answering auditor questions and providing copies of documentation and reviewing procedures with the sponsor.

5.4 BQA personnel are responsible for processing documentation requests, making requested copies, when appropriate, and for reviewing documents to ensure they are appropriate and relevant to the sponsor's question prior to presentation to sponsor.

5.5 Sponsors who intend to audit BDP processes are responsible for:

5.5.1 Communicating their request for an audit.

5.5.2 Identifying the scope of the audit.

5.5.3 Proposing an audit agenda.

5.5.4 Adhering to the audit agenda during the audit unless a change to the agenda has been negotiated between the sponsor and BDP management.

5.5.5 Signing a confidentiality agreement with the NCI/BDP prior to the audit.

5.6 The BDP Point of Contact is responsible for:

5.6.1 Assisting sponsors in developing the scope, timing, and proposed agenda for the audit.

5.6.2 Receiving sponsor auditors at Security and escorting them to the audit location.

6.0 Procedure

6.1 Requesting an Audit

6.1.1 Requests for an audit by a sponsor may be requested through the NCI's Biological Resource Branch or directly to the BDP management.

6.1.2 A request for an audit of the BDP must be received at least two weeks in advance of the proposed date of the audit. However, earlier notification is much preferred.

6.1.2.1 Requests must be submitted in writing (E-mail contact, facsimile, or formal written letter).

6.1.2.2 Requests must be transmitted to one of the following BDP Directors who will forward the request to the BQA Audit Manager.

- Program and Technical Director of the BDP.
- Director of Regulatory Compliance.

6.1.3 The sponsor must also follow-up this initial contact with a proposed audit agenda that outlines:

6.1.3.1 Purpose of the audit (type of audit to be conducted).

6.1.3.2 Sponsor auditors (or contracted third-party auditors) assigned to the audit.

6.1.3.3 Proposed audit date(s).

6.1.3.4 Areas to be toured.

6.1.3.5 Documentation requested by the sponsor as “read-ahead” data.

6.1.3.6 Documentation to be available during the audit.

6.1.3.7 Suggested BDP personnel to be available during the audit.

6.2 Audit Authorization

6.2.1 Appropriate BDP and NCI-BRB management will authorize the audit including the scope of the audit, timing, the proposed agenda, and the Points of Contact for either BDP (or NCI) and the sponsor. (Refer Form 21701-01, Audit Authorization.)

6.2.2 The audit authorization must be complete before the audit commences.

6.2.3 BDP management will accommodate reasonable requests for audits whenever possible. However, the timing and scope of audits shall be scheduled so as not to interfere with production activities or the mission of the BDP.

6.2.4 Changes to the audit scope or agenda made after the audit has started will require additional authorization by BDP Management.

6.3 Preparation for the Audit

6.3.1 Upon notification of an audit, BDP auditing staff will contact the sponsor directly or work through the NCI contact to:

6.3.1.1 Confirm the audit dates.

6.3.1.2 Arrange a meeting area

6.3.1.3 Compile documentation.

6.3.1.4 Ship “read-ahead” documentation, which must be authorized by a distribution form (***SOP 21417, BDP Distribution Record for Documents).***

6.3.1.5 Provide details of the audit to other involved BDP staff members.

6.3.1.6 Contact Security personnel to notify them of the auditor(s) planned date(s) of arrival.

6.4 Audit Execution

6.4.1 Arrival

6.4.1.1 The BDP facility is located at the Advanced Technology Research Facility (ATRF), Frederick, Maryland and the following security measures must be observed while the auditors are on the campus.

- Auditors must go directly to the Security Desk located in the main lobby of the ATRF and obtain a visitor's badge.
- Auditors shall be escorted to the meeting area by either the NCI Point of Contact or by designated BDP personnel.
- Auditors must be always escorted while in BDP-operated facilities by either the NCI contact or BDP personnel.

6.4.2 Meeting Area

6.4.2.1 The auditor(s) will be escorted to a pre-arranged meeting area. This area will be large enough to allow several sponsor auditors and several BDP personnel to conduct the audit.

- Due to space limitations and other scheduled activities within the BDP, audit meeting areas may change from day to day.

6.4.2.2 Sponsor Auditors and BDP personnel will be required to sign an attendance log to indicate that they were present during the opening meeting. (Refer to Form 21701-02, Audit Attendance Log)

6.4.3 Documentation

6.4.3.1 Copies of organizational charts, SOP index, facility floor plans, and similar documentation will be available for review by the auditor(s).

6.4.3.2 Relevant documentation requested, either previously or during the audit, will be bought to this meeting area for review. BQA will maintain a log of documentation requested, provided, and reviewed during the audit. (Refer to Form 21701-03, Documentation Request Log.)

6.4.3.3 The Director of Regulatory Compliance, BQA will review requests for sponsor copies of documentation, which will be retained by the auditors, on a case-by-case basis.

6.5 Touring Facilities

6.5.1 Auditor(s) will be escorted by BQA personnel on all tours.

6.5.2 Auditor(s) will be required to follow safety, personnel gowning, and other requirements for entering work areas.

6.5.3 This may include, but is not limited to, wearing safety glasses, lab coats, foot coverings and hair coverings.

6.5.4 Auditor(s) may not be allowed into some areas of the facility based on the activities occurring at the BDP.

6.5.5 Auditors may not enter production areas while work is occurring since their presence may interfere with production work. The request will be reviewed with the facility supervisor or manager during the tour to determine if accommodations can be made. Auditors shall be encouraged to view laboratory activities through windows, when available.

6.5.6 Auditors are not allowed in the Class 100 clean room suites or other aseptic areas. Windows allow viewing of these areas.

6.5.7 Auditors are not allowed into the Virus Production Facility (VPF) suite during active project campaigns. Closed circuit TV in this area allows viewing of operations.

6.5.8 Auditors may observe staff conducting operations and may, at the discretion of BDP management, interview staff during the tour if operations are not interrupted or that employees are not distracted from performing their job responsibilities. Their supervisor or manager must be present, when possible.

6.5.9 Auditors shall be encouraged to immediately bring to the attention of the BDP escort any adverse findings or observations that are noted.

6.6 The Exit Summary (Closeout Meeting)

6.6.1 An exit meeting will be scheduled at the conclusion of the audit. Relevant attendees will be invited to attend and sign Form 21701-04 – Closing Meeting Attendance Log. Minutes of this exit summary will be taken by BQA.

6.6.2 No commitments for corrective/preventative actions will be made during the audit or at the closeout meeting without senior management and/or NCI approval.

6.7 Audit Follow-up

6.7.1 Attendees of the close-out meeting (de-briefing meeting) will sign the Attendance Log.

6.7.2 A written audit response to the sponsor's audit findings will be provided if requested by the sponsor after the receipt of a written audit report. Typically, audit responses are available to the sponsor within 60 days of submitting the written audit report.

6.8 Sponsor Considerations for Conducting Audits of the BDP

6.8.1 For general oversight of CGMP compliance, each of the various subject areas for GMP Compliance may be audited only once per year by the same sponsor regardless of the number of projects performed for the sponsor.

6.8.2 More than one audit per year is possible if the scope of the different audits does not cause the same subject area to be audited more than once/year, and approvals are obtained from the Director of Regulatory Compliance and the Program and Technical Director.

6.8.3 Once a quality system element or document is reviewed by the sponsor and comments have been addressed by the BDP, the system element or document will be considered as acceptable to the sponsor by the BDP. Subsequent reviews and comments by sponsor auditors, therefore, may not be addressed unless a critical system element or critical documentation flaw is revealed by the subsequent review. Any requests to re-audit will usually be refused unless extenuating circumstances are evident, such as multiple out-of-specification results, significant validation issues, significant deviations, or the system element or document is significantly revised.

6.8.4 Documentation reviewed by the sponsor (SOPs, COAs, MPRs, etc.) may be reviewed for content and overall compliance level to GMPs; however, proposed changes to the approved BDP documentation format may not be implemented.

6.8.5 Other types of audits (Documentation Review, For Cause, etc.) will be arranged only with the approval of the Director of Regulatory Compliance and/or Program and Technical Director.

6.8.6 Sponsor auditor(s) or third-party contract auditors must not be former employees of the BDP. This is to prevent any bias (either favorable or unfavorable) by the auditor. Refer to the American Society for Quality "Code of Ethics" and the Government Auditing Standards (GAO-02-340G), Section 1.26.

6.9 Timing of Audit

6.9.1 An audit of the BDP facility and quality system elements should be conducted prior to the approval of a contract, when possible.

7.0 Documentation

7.1 BQA will create an audit file for each sponsor audit conducted.

7.2 This file will contain:

7.2.1 Audit Authorization Form (this documents the scope of the audit).

7.2.2 Audit agenda as supplied by the sponsor.

7.2.3 Attendance logs

7.2.4 List of documentation reviewed and or copied.

7.2.5 Notes taken during the audit.

7.2.6 Minutes of the closeout meeting.

7.2.7 Sponsor's written audit report detailing any audit findings.

7.2.8 BDP response to the audit.

7.2.9 Any other documentation associated with the audit.

8.0 References and Related Documents

8.1 **SOP 21417** *BDP Distribution Record for Documents*

8.2 American Society for Quality "Code of Ethics" and the Government Auditing Standards (GAO-02-340G),

9.0 Change Summary