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1.0 Purpose

This document describes the policies and the operational procedures governing contract manufacturing by the Frederick National Laboratory Cancer Research (FNLCR) / Leidos Biomedical Research, Inc., Biopharmaceutical Development Program (BDP) for institutions other than the FNLCR-BRB. The BDP works cooperatively with Sponsors to develop and manufacture products appropriate for Phase I/II investigational use.

2.0 Scope

This procedure applies to requests from the NCI-BRB to the BDP for the manufacture of biologics for third parties or Sponsors and the information, communications, and actions that are permitted and provided between the third party and the BDP. This document does not apply to work performed directly for the BRB.

3.0 Policy

It is the policy of the BDP to:

- Comply with CGMP regulations as they pertain to the manufacture of biologics/drugs for Phase I/II investigational use.
- Encourage the Sponsor to perform a CGMP audit of those BDP systems and facilities that are relevant to the Sponsor's project. See ***SOP 21701, Management of Sponsor Audits***.
- Obtain approval by the Sponsor, upon request, prior to the use of Sponsor related Master Production Records (MPR), Master Specifications, product-specific SOPs, and critical changes.
- Maintain active and timely communications with the Sponsor for significant deviations, failures, etc., if requested.

- Accommodate, upon request, a Sponsor's "person-in-the-plant" (PIP) as is deemed reasonable by the BDP (Sponsor personnel are not allowed in aseptic fill/finish areas).
- Provide a copy of the completed Batch Production Record to the Sponsor for review and other additional records as specified, if requested.
- Hold regular project team meetings with the Sponsor (not to exceed 1 per month, unless it is deemed critical).
- Release the lot based on conformance to mutually-approved MPRs and specifications, and mutually-agreed changes and corrective actions to deviations and non-conformances.
- Perform production on a "good faith" effort.
- Be solely responsible for the management of development, production, and testing efforts assigned to the BDP.

4.0 Authority and Responsibility

4.1 The Director of Regulatory Compliance, BDP (with responsibility for Quality Assurance) has the authority and responsibility for:

4.1.1 Implementation of this procedure.

4.1.2 Working with Sponsor Management to:

4.1.2.1 Communicate with the Sponsor regarding the Quality System in place at the BDP, including, but not limited to:

- The identity, purity, strength, quality, potency, release and in-process specifications for the biologic/drug product.
- Documentation of the production process.
- Reporting changes to the production process (as required by 21 CFR 601.12) as appropriate for a Phase I/II investigational-use product.
- QA oversight and change control for master and batch production records.
- Process Analytics (PA) methodology as it relates to the production process.
- Labeling.
- Validation, maintenance, and proper functioning of equipment and systems that pertain to the Sponsor's project.
- Environmental and other required monitoring.
- Training of personnel.

4.1.2.2 Negotiate the areas of authority and responsibility for quality oversight and regulatory compliance by the BDP and the sponsor organization, and document those decisions in the Sponsor Contract or the Sponsor Quality Agreement.

4.1.3 Providing the quality oversight and regulatory compliance needed to meet the responsibilities defined in the Sponsor Contract or Sponsor Quality Agreement.

4.1.4 Designating BDP points of contact.

4.2 Sponsor Management is responsible for:

4.2.1 Working with BDP Management to clearly define the areas of authority and responsibility for both the BDP and the Sponsor organization including, but not limited to:

- The identity, purity, strength, quality, potency, release and in-process specifications for the biologic/drug product.
- Development of the production process.
- QA oversight and change control for master and batch production records.
- PA methodology as it relates to the production process.
- Labeling.
- Validation, maintenance, and proper functioning of equipment and systems that pertain to the Sponsor's project.
- Environmental and other required monitoring.
- Training of personnel.

4.2.2 Providing the timely oversight needed to meet the responsibilities defined in the Sponsor Contract or Sponsor Quality Agreement.

4.2.3 Designating points of contact

4.2.4 Working within the framework of this SOP.

4.3 The Director of Regulatory Compliance or designee is responsible for development of the Quality Agreement between BDP and the Sponsor, if applicable.

5.0 Introduction

The BDP provides biopharmaceutical development and manufacturing services, at the request of the NCI-BRB, for various Sponsors to develop and manufacture GMP products with the safety, identity, purity and strength appropriate for a Phase I/II clinical biologic/drug product (CGMP).

The BDP is prepared to provide complete oversight of the technical, quality, and regulatory requirements related to the development and manufacture of a biologic drug product. In some situations, the Sponsor may choose to exercise additional oversight responsibilities for some portions of the project. Sponsors may also request that a Sponsor representative (person in the plant) be on site during certain manufacturing operations to meet these oversight responsibilities.

The division of authority and responsibility between the Sponsor organization and the BDP are defined and documented in the Sponsor Contract with the BDP and/or in a Quality Agreement with the Sponsor. A clear and documented designation of the authority and responsibility for the various aspects of a project enhances the efficiency of the general process and ensures that both organizations apply appropriate resources to the project.

6.0 Procedure for BDP Oversight Activities

6.1 Development of the Sponsor Contract or Quality Agreement

6.1.1 The Quality Agreement is negotiated between BDP management and Sponsor management and defines the authority and responsibility for the activities described in Section 3.0.

6.1.2 The results of this negotiation must be documented either in the contract between the BDP and the Sponsor or in the BDP's Quality Agreement with the sponsor.

6.1.3 These documents must be signed by the following persons or their delegates:

BDP:

- Director of Regulatory Compliance, and
- Program and Technical Director

BRB:

- Chief, Biological Resources Branch

Sponsor:

- Director of Quality Assurance (or Regulatory Affairs), and
- Project Head

6.1.4 Changes to the agreed-upon authority and responsibility between the BDP and the Sponsor may require a revision to the contract or to the Quality Agreement.

6.1.5 The Sponsor Contract or Quality Agreement shall specify the level of oversight the Sponsor requires for approval of project-specific documents. Unless otherwise specified, Sponsor approval for project-specific documents will not be required.

6.2 Quality System Processes and Documentation

6.2.1 The BDP is responsible for maintaining effective Quality System processes and documentation (appropriate for the manufacture of Phase I/II clinical biologic/drug products).

6.2.2 Sponsor representatives are expected to review and comment on BDP Quality System processes and documentation.

6.2.3 Sponsor representatives may propose changes to Quality System processes and documents. Changes to Quality System processes and documents will be made only if agreed to and authorized by the BDP before implementation.

6.3 Project-Specific Operations and Documentation

6.3.1 The BDP develops and manufactures Sponsor products within the framework of the existing BDP Quality System.

6.3.2 Project-specific processes and documentation may be developed to meet the requirements of the project.

6.3.2.1 Documents shall be developed to be consistent with BDP's Quality System requirements. Approved BDP formats and templates shall be used in the development of project-specific documents.

6.3.2.2 The BDP documents that describe the Sponsor's project-specific processes shall be available for review and approval by the Sponsor if requested.

6.4 Management of Planned and Unplanned Deviations

6.4.1 The BDP has responsibility and authority for the review, disposition, and follow-up of deviation reports.

6.4.2 Sponsors will be notified of deviations affecting their projects and their disposition in a timely manner as specified in the Sponsor Contract or Quality Agreement.

6.4.3 Sponsors may also request that copies of deviations to be forwarded to them in a timely manner as specified in the Sponsor Contract or Quality Agreement.

6.5 Scheduling and Approval to Proceed Through Each Phase of Manufacturing

6.5.1 The BDP has the authority to approve the continuance of the project through each phase of processing. This decision will be made based on the technological readiness of the process, satisfactory in-process data, and the appropriate level of GMP compliance.

6.6 Lot Release Decisions

6.6.1 Unless otherwise specified in the Sponsor Contract or Quality Agreement, the BDP has the authority for the final lot release of the product. Sponsors shall be encouraged to establish their own additional product release subsequent to the BDP release.

6.6.2 The BDP manages lot release decisions according to ***SOP 21002, Product Release.***

6.6.3 Product release includes:

6.6.3.1 BQA review of the Batch Production Record(s)

6.6.3.2 BQA review/approval of Certificate of Analysis(s)

6.6.3.3 Release approval by the Director of Regulatory Compliance or BQA designee

6.7 Auditing

6.7.1 The BDP encourages auditing of the BDP's quality system, facility, and operations that are relevant to the Sponsor's project prior to contract or quality agreement approval, if possible. Auditing will be managed according to SOP ***21701, Management of Sponsor Audits.***

6.8 Person in the Plant (PIP) Management

6.8.1 The Quality Agreement and/or Sponsor Contract will describe the responsibilities of the PIP.

6.8.2 The PIP will not direct plant activities or BDP operations.

6.8.3 The PIP is permitted and encouraged to comment on activities observed.

6.8.4 The BDP will allow access to the facility at any reasonable time requested for the purpose of:

6.8.4.1 Observing manufacturing operations specific to the Sponsor's product.

6.8.4.2 Assisting in problem solving.

6.8.4.3 Facilitating communications between the Sponsor and the BDP.

6.8.5 The Sponsor may not assign former employees of the BDP to a BDP project as a PIP.

6.8.6 The PIP will be provided with a BQA escort (as needed) for areas they wish to visit to directly observe operations.

6.8.7 The PIP will not be allowed access to the following areas:

- The PIP will not be allowed into the fill/finish clean room suites. This area has a real-time video camera (closed circuit television) that allows viewing of operations.
- The PIP will not be allowed into the Virus Production Facility (VPF) Suite during active product campaigns. This area has a real-time video camera (closed circuit television) for watching operations in the VPF.

6.8.8 The presence of the PIP must not interfere in any way with the operations being observed.

6.9 Change Control

6.9.1 The BDP is responsible for the management of a change to Quality System policies and procedures.

6.9.2 Sponsor management will be informed of significant changes to Quality System policies and procedures that may have a direct impact on the safety, identity, purity, and strength of their product prior to the change, if specified in the Sponsor Contract or Quality Agreement.

6.10 Process Validation

6.10.1 Process validation is maintained for aseptic filling in specific container/closure systems.

6.10.2 Unless otherwise specified, the use of BDP standard containers and closures will be assumed.

6.10.3 The proposed use of “non-standard” containers or closures must be brought to the attention of BDP management early in the project to evaluate the need for additional validation studies.

6.10.4 Use of non-standard containers or closures must be documented in the Sponsor Contract or Quality Agreement.

6.10.5 Except for aseptic media fill and related validations, process validation is not performed for Phase I/II products.

6.10.6 Requests to perform process validation must be discussed with BDP management, and any agreement for BDP to perform additional validation must be documented as part of the Sponsor Contract or Quality Agreement.

6.11 Test Method Validation

6.11.1 Requests to perform additional test method validation must be discussed with BDP management, and any agreement for BDP to perform additional validation must be documented as part of the Sponsor Contract or Quality Agreement.

6.12 Communications between the Sponsor and the BDP (Points of Contact)

6.12.1 In order to provide effective and clear communications between the Sponsor and the BDP, the following must be observed.

- The Sponsor can designate no more than three individuals at the Sponsor site to serve as points of contact for BDP communications.
- The BDP will also designate no more than three individuals as points of contact with the Sponsor.
- It is recommended that these individuals represent the following groups:
    - Business Operations
    - Technical Operations
    - Regulatory/Quality Assurance Operations

6.12.2 Both the Sponsor and the BDP will provide verbal and written communications as necessary to meet the needs of the project. Follow-up of important verbal communications in writing will ensure clarity of issues for both parties.

7.0 Definitions

7.1 Person in the Plant (PIP) – A Sponsor's representative that is on site at the production facility for the purposes of observing operations in real time.

7.2 Quality Agreement – Clarifies the regulatory compliance and quality aspects of the business relationship. It outlines in detail the expectations and responsibilities of a quality or regulatory nature between the Sponsor and the BDP.

8.0 Change Summary