Frederick National Laboratory for Cancer Research

BIOPHARMACEUTICAL DEVELOPMENT PROGRAM

SOP Title:	**Quality Assurance Operations, Responsibilities, and Authority**
SOP Number:	**21006**
Revision:	**05**

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1. PURPOSE

This Standard Operating Procedure (SOP) defines Quality Assurance (QA) operations, responsibilities, and authority for maintaining appropriate quality systems to ensure compliance to Current Good Manufacturing Practice (CGMP) regulations as applicable to the manufacture and testing of pre-clinical and Phase I, II, and non-pivotal Phase III Clinical Products.

2. SCOPE

This procedure applies to the functions of QA for the Biopharmaceutical Development Program (BDP), regarding QA oversight of CGMP operations. This document applies to personnel, raw materials, testing, facilities, equipment, manufacturing, validation, document control, and regulatory submissions. This procedure applies to members of the Quality Assurance Department who are responsible for overseeing the designated quality system activities.

3. RESPONSIBILITIES

3.1 Director, Regulatory Compliance

- Defines this procedure.

3.2 Quality Assurance Department

- Designs and maintains quality systems that ensure compliance to CGMP (21 CFR 211 and 21 CFR 600) and applicable GLP (21 CFR 58) regulations,

guidance's, and industry standards relating to the manufacture and testing of biologics and biopharmaceuticals for pre-clinical and Phase I & II clinical use.

- Ensures that adequate personnel, facilities, utilities, equipment, procedures, and documentation are available for the execution of CGMP and GLP activities.
- Ensures contract manufacturing and testing facilities meet appropriate GLP, CGMP, or other compliance level as applies to the work they are expected to perform.

3.3 BDP Employees

- Understands and complies with this and other Quality System SOPs.

4. DEFINITIONS

- **21 CFR 58, Good Laboratory Practices**

  The Good Laboratory Practice (GLP) regulations prescribe good laboratory practices for conducting non-clinical laboratory studies that support, or are intended to support, applications for research or marketing permits for products regulated by the FDA. Applicable nonclinical laboratory studies include *in vivo* or *in vitro* experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. Compliance to these regulations is intended to assure the quality and integrity of the safety data submitted to the FDA.

  Depending on the project's scope, BDP may provide material that can be used in a GLP study (e.g., an IND-directed toxicology study). BDP also provides analytical data associated with the material, with may assist the Sponsor in meeting the requirements under 21 CFR 58.105 (test and control article characterization).The BDP may also use contract testing facilities for analytical testing that falls under the definition of nonclinical laboratory study above (e.g., *in vivo* adventitious agent testing).

  The Good Laboratory Practice regulations (21 CFR 58) present the requirements for the control of the execution of animal safety testing. There are few specific GLP regulations that must be applied to the manufacture of GLP/pre-clinical products (**see 21 CFR 58, 105(a) Test and Control Article Characterization**). Some of the controls that are prescribed for the testing of product can also be applied to the manufacture of the product that will be tested. The BDP applies GLP controls in the manufacture of pre-clinical materials as appropriate, as per **SOP 21900 - Expectations for the Production of Product for Toxicology Testing**.

- **21 CFR 210/211, Good Manufacturing Practice for Finished Pharmaceuticals**

  The Federal Food, Drug and Cosmetic Act (Section 501(a)(2)(B)) requires that all drugs (including bulk drugs and finished drugs) be manufactured, processed, packaged and held in accordance with current good manufacturing practices (CGMP).

  21 CFR 211.22 Responsibilities of quality control unit.

  21 CFR 211.22(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

  21 CFR 211.22(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.

  21 CFR 211.22(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

  21 CFR 211.22(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

  The regulations in 21 CFR Part 211 contain the minimum current good manufacturing practices for the preparation of drug and biologic products for administration to humans or animals to ensure the safety, identity, strength, quality, and purity of drug products. The BDP operates in compliance with the requirements of this part as appropriate for Phase I and II clinical materials.

- **21 CFR 600, Biological Products: General**

  The regulations in 21 CFR 600 contain the minimum current requirements for biological products including requirements for the drug product, personnel, facilities, equipment, records, reporting of errors, shipping and inspections.

  Generally, because many of the BDP drug products are biologics, the BDP complies with the requirements of this part as appropriate for Phase I and II clinical materials.

- **21 CFR 610, General Biological Products Standards**

  The regulations in 21 CFR 610 contain the minimum current requirements for general biological product standards. Generally, because many BDP drug products are

biologics, the BDP complies with the requirements of this part as appropriate for Phase I and II clinical materials.

- **21 CFR 1271, Human Cells, Tissues, and Cellular and Tissue-Based Products**

  The regulations in 21 CFR 1271 contain the minimum requirements for human cells, tissues, and cellular and tissue based products (HCT/Ps). There is significant overlap between therequirements of 21 CFR 1271 and 21 CFR 211 and, in many cases, the same manufacturing practice will meet the requirements of both regulations. For cell therapy products, BDP complies with the requirements of this part as are appropriate for investigational products.

5. OVERVIEW

5.1 QA is responsible for ensuring that appropriate systems are in place and are used for the manufacture of pre-clinical and CGMP products. This includes product produced within the BDP and product produced for the BDP by contract manufacturers. QA has the responsibility to assure that personnel, facilities, equipment, materials, processes, and procedures are appropriate to ensure the safety, identity, strength, quality, and purity of drug products. Changes to existing systems or the development of new systems are made in response to detected or perceived system deficiencies, additional process knowledge, technological advancements, or changes in the regulatory requirement. These responsibilities require QA oversight of systems that produce, store, and test product, including the methods and controls, the facilities and equipment, the people that execute the systems, and the documentation that demonstrates that the systems are operating as designed.

5.2 Specifically, QA has the authority and responsibility to review and accept or reject the following:

- The design, engineering, and physical attributes of the facility and the equipment/utilities associated with the manufacturing of materials.
- Manufacturing and testing procedures and specifications.
- Changes to already approved facilities, equipment, processes, procedures, and specifications.
- Master and batch production records and associated supporting documents.
- Raw materials, in-process materials, final product, packaging and labeling.
- Contract Manufacturers involved in GMP production activities.
- Quality Control (QC) testing procedures and records including contract testing facilities.
- The investigation and disposition of adverse quality events such as deviations, failures, out-of-specifications (OOS), material review board

(MRB), out-of-tolerance (OOT), complaints, adverse audit observations, and related occurrences.
- Release of products.

6. ORGANIZATION

6.1 Frederick National Laboratory for Cancer Research (FNLCR)

The National Cancer Institute (NCI) Division of Cancer Treatment and Diagnosis, Developmental Therapeutics Program, Biological Resources Branch (BRB) provides oversight of the Leidos Biomedical Research, Inc., Biopharmaceutical Development Program (BDP).

6.2 Leidos Biomedical Research, Inc.

Leidos Biomedical Research, Inc. manages the Operation and Technical Support program contract for the FNLCR.

6.3 Biopharmaceutical Development Program

The BDP is a directorate within Leidos Biomedical Research, Inc., and has been designed as a biopharmaceutical resource for the development and manufacture of biopharmaceuticals, cell and gene therapy products, and other biologics in compliance with CGMP regulations for Phase I/II and non-pivotal Phase III clinical trials, and preclinical testing. The Program and Technical Director heads the BDP. BDP Departments, except Quality Assurance, report to this director. QA reports to the Director, Clinical Research Directorate. This is a separate reporting structure from the manufacturing operations of the organization.

6.4 QA fulfills the FDA requirement that there be an independent function responsible for ensuring compliance with CGMPs and related regulations and expectations. QA is divided into six main areas that are overseen by the Director of Regulatory Compliance. Each area is under the control of either the Director of Regulatory Compliance, Associate Director of Regulatory Affairs (RA), or the QA Managers (See functional organizational chart, Attachment 1). The six areas are listed below:

- Regulatory Affairs
- Quality Management
- QA Compliance & Auditing
- QA GMP Documentation
- QA Quality Engineering and Validation
- BDP Training

7. QA RESPONSIBILITIES AND AUTHORITY

7.1 Regulatory Affairs (Associate Director Regulatory Affairs)

Regulatory Affairs is responsible for providing Pre-Investigational New Drug (IND) Meeting support and documents; Chemistry, Manufacturing, and Control (CMC) sections of INDs; CMC amendments; responses to Regulatory Agency CMC comments; and general regulatory support. Regulatory Affairs also maintains a Type V Drug Master File for the BDP facilities with the FDA/CBER.

7.2 Quality Management (Director, Regulatory Compliance). Quality Management has the authority and responsibility for, or provides oversight for:

- Final approval for the release of products for use in humans
- Only the Director, Regulatory Compliance, or other QA/RA designee, has the authority to release products for use in humans.
- The final disposition of adverse quality events.
- Quality oversight of program GMP projects.
- Managing and driving continuous quality improvements.
- Risk management and mitigation.

7.3 QA Managers are responsible for:

- Change control management.
- Conducting internal audits and external vendor audits of contract manufacturers and service providers.
- Reviewing, dispositioning, and trending deviations (both planned and un-planned).
- Reviewing and approval of raw material specifications. Dispositioning of raw materials, components, manufacturing materials, in-process materials, packaging materials, and final product.
- Managing product, complaint, and process investigations, out-of-specification investigations and, as necessary, deviations and unexpected events.
- Conducting manufacturing area releases for GMP manufacturing operations.
- Reviewing and dispositioning manufacturing specifications.
- Reviewing manufacturing records for compliance to specifications and CGMP requirements.
- Performing release activities for raw materials, cell and viral banks, and product.
- Reviewing and dispositioning procedures (SOPs).

7.4 BQA Documentation functions include:

- The creation, distribution, control, retrieval, archiving, and destruction of CGMP documentation and records.
- Management of Standard Operating Procedures, Master Production and Control Records, Batch Production Records, Validation Protocols and packages, Master Specifications, Certificates of Analysis, Logbooks, Laboratory Notebooks, Project Files, and related documents.

7.5 Quality Engineering and Validation (Manager, Quality Engineering/Validation).

The Quality Engineering and Validation Department is responsible for:

- Participating in the design and construction planning for facilities and equipment.
- Oversight of GMP facilities drawings, pest control, cleaning, maintenance, and other facilities related GMP functions.
- Oversight of validation, qualification, calibration and preventative maintenance of utilities and process equipment.
- Oversight of process validations to include Validation Master Plan, airflow visualization, aseptic filling and sterile transfer.
- Oversight of computer and software validation, cleaning validation, and shipping validation.
- Managing Engineering Events and related procedures.
- Reviewing environmental, water, and utility monitoring data for generation of associated production clearance authorizations and compliance to relevant guidelines. Generating annual utility certification packages.
- Participating in investigations for non-conforming events.

7.6 BDP Training (Director Regulatory Compliance and QA Managers)

QA is responsible for coordinating the training of employees in specific SOPs and skills required for job responsibilities, conducting cGMP training, and maintaining documentation of training.

8. RESOURCES

8.1 QA Facilities

8.1.1 QA offices are in the [redacted], Sections E (second floor) and B (third floor). These areas are comprised of offices and workstations that allow space for PC stations and work files.

8.1.2 Hardcopy documentation is maintained/archived in a high-density secure file system in a separate, locked area of the ATRF, Section E, Second Floor. The high-density file system is used to facilitate retrieval of filed documents (SOP, MPR, BPR, MS, COA, Project Files, Qualification and Validation documents, completed QCTRs, etc.). Additional record storage areas are located at contract off-site storage locations.

8.2 Electronic Storage and Management Systems

8.2.1 Electronic working versions of documentation (Word, PDF, etc.) are maintained on secure servers. These are accessed and managed by those responsible for the creation, modification, and control of cGMP documents.

8.2.2 Electronic databases such as Access and SQL Server and applications utilizing these database systems, such as MasterControl, Blue Mountain Regulatory Asset Manager (Calibration Manager), etc., are used to manage the various operational and quality systems of the BDP. Data managed and accessed in this manner include:

- Documents (SOPs, MPRs, Validation Protocols, etc.]
- Validation program
- Calibration program
- Equipment
- Environmental and water monitoring
- Training program

8.3 QA Personnel

QA personnel are identified per the current organizational chart.

8.4 Standard Operating Procedures

8.4.1 Procedures have been established to maintain the systems and documentation required by CGMP regulations. A complete listing of QA SOPs is maintained in QA.

8.4.2 Authorized and approved SOP’s are maintained in the eDMS.

9. REFERENCES AND RELATED DOCUMENTS

Document Number	Title
21900	Expectations for the Production of Product for Toxicology Testing
21 CFR 211.22	Responsibilities of Quality Control Unit
21 CFR 211.100	Written Procedures
21 CFR 211.160	Laboratory Controls
21 CFR 58	Good Laboratory Practices
21 CFR 600	Biological Products: General
21 CFR 610	General Biological Products Standards
21 CFR 1271	Human Cells, Tissues, and Cellular and Tissue-Based Products

10. ATTACHMENTS

Attachment 1 Quality Assurance Functional Organizational Chart

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