Frederick National Laboratory for Cancer Research, Frederick, MD

Biopharmaceutical Development Program

Standard Operating Procedure

Title: Quality Assurance Operations, Responsibilities, and Authority

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1.0 Purpose

This Standard Operating Procedure (SOP) defines Biopharmaceutical Quality Assurance (BQA) 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.

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

2.0 Scope

This procedure applies to the functions of BQA for the Biopharmaceutical Development Program (BDP), regarding BQA oversight of CGMP and Good Laboratory Practice (GLP) 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.

3.0 Authority and Responsibility

3.1 The Director, Quality Assurance has the authority to define this procedure.

3.2 The BQA Department is responsible for the following:

3.2.1 Designing and maintaining quality systems that ensure compliance to CGMP (21 CFR 211 and 21 CFR 600) and 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.

3.2.2 Ensuring that adequate personnel, facilities, utilities, equipment, procedures, and documentation are available for the execution of CGMP and GLP activities.

3.2.3 Ensuring that 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 It is the responsibility of all BDP employees to understand and comply with this and other Quality System SOPs and procedures.

4.0 Overview

4.1 BQA 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. BQA 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 BQA 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.

4.2 Specifically, BQA has the authority and responsibility to review and accept or reject the following.

4.2.1 The design, engineering, and physical attributes of the facility and the equipment/utilities associated with the manufacturing of materials.

4.2.2 Manufacturing and testing procedures and specifications.

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

4.2.3 Changes to already approved facilities, equipment, processes, procedures, and specifications.

4.2.4 Master and batch production records and associated supporting documents.

4.2.5 Raw materials, in-process materials, final product, packaging and labeling.

4.2.6 Contract Manufacturers involved in GMP production activities.

4.2.7 Quality Control (QC) testing procedures and records including contract testing facilities.

4.2.8 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.

4.2.9 Release of products.

5.0 Organization

5.1 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).

5.2 Leidos Biomedical Research, Inc.

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

5.3 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. BQA reports to the Director, Clinical Research Directorate. This is a separate reporting structure from the manufacturing operations of the organization.

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

5.4.1 Regulatory Affairs

5.4.2 Quality Management

5.4.3 BQA Compliance & Auditing

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

5.4.4 BQA GMP Documentation

5.4.5 BQA Quality Engineering and Validation

5.4.6 BDP Training

6.0 BQA Responsibilities and Authority

6.1 Regulatory Affairs (Director Regulatory Affairs)

6.1.1 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.

6.2 Quality Management (Director, Quality Assurance). Quality Management has the authority and responsibility for, or provides oversight for:

6.2.1 Final approval for the release of products for use in humans

6.2.1.1 Only the Director, Quality Assurance, or other QA/RA designee, has the authority to release products for use in humans.

6.2.2 The final disposition of adverse quality events. (see Section 4.2.8)

6.2.3 Quality oversight of program GLP & GMP projects.

6.2.4 Managing and driving continuous quality improvements.

6.2.5 Risk management and mitigation.

6.3 BQA Managers are responsible for:

6.3.1 Change control management.

6.3.2 Conducting internal audits and external vendor audits of contract manufacturers and service providers.

6.3.3 Reviewing, dispositioning, and trending deviations (both planned and un-planned).

6.3.4 Reviewing and approval of raw material specifications. Dispositioning of raw materials, components, manufacturing materials, in-process materials, packaging materials, and final product.

6.3.5 Managing product, complaint, and process investigations, out-of-specification investigations and, as necessary, deviations and unexpected events.

6.3.6 Conducting manufacturing area releases for GMP manufacturing operations.

6.3.7 Reviewing and dispositioning manufacturing specifications.

6.3.8 Reviewing manufacturing records for compliance to specifications and CGMP requirements.

6.3.9 Performing release activities for raw materials, cell and viral banks, and product.

6.3.10 Reviewing and dispositioning procedures (SOPs).

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6.4 BQA Documentation Manager functions include:

6.4.1 The creation, distribution, control, retrieval, archiving, and destruction of GLP and CGMP documentation and records.

6.4.2 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.

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

The Quality Engineering and Validation Department is responsible for:

6.5.1 Participating in the design and construction planning for facilities and equipment.

6.5.2 Oversight of GMP facilities drawings, pest control, cleaning, maintenance, and other facilities related GMP functions.

6.5.3 Oversight of validation, qualification, calibration and preventative maintenance of utilities and process equipment.

6.5.4 Oversight of process validations to include Validation Master Plan, airflow visualization, aseptic filling and sterile transfer.

6.5.5 Oversight of computer and software validation, cleaning validation, and shipping validation.

6.5.6 Managing Engineering Events and related procedures.

6.5.7 Reviewing environmental, water, and utility monitoring data for generation of associated production clearance authorizations and compliance to relevant guidelines. Generating annual utility certification packages.

6.5.8 Participating in investigations for non-conforming events.

6.6 BDP Training (BQA Director and BQA Managers)

6.6.1 BQA 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.

7.0 Resources

7.1 BQA Facilities

7.1.1 BQA offices are located in the [redacted], Sections [redacted] [redacted] Floor. These areas are comprised of offices and workstations that allow space for PC stations and work files.

7.1.2 Hardcopy documentation is maintained/archived in a high-density secure file system in a separate, locked area of the [redacted], Section [redacted], [redacted] 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.

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7.2 Electronic Storage and Management Systems

7.2.1 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 GLP and CGMP documents.

7.2.2 Electronic databases such as Access and SQL Server and applications utilizing these database systems, such as TrackWise, 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:

7.2.2.1 Documents (SOPs, MPRs, Validation Protocols, etc.]

7.2.2.2 Validation program

7.2.2.3 Calibration program

7.2.2.4 Equipment

7.2.2.5 Environmental and water monitoring

7.2.2.6 Training program

7.3 BQA Personnel

7.3.1 BQA personnel are identified per the current organizational chart.

8.0 Standard Operating Procedures

8.1 Procedures have been established to maintain the systems and documentation required by GLP and CGMP regulations as listed in Attachment 2 (partial listing of policies and selected SOPs). A complete listing of BQA SOPs is maintained in BQA.

8.2 Authorized and approved SOP's are maintained on file in BQAD.

9.0 Definitions

9.1 **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. Compliance to these regulations is intended to assure the quality and integrity of the safety data submitted to the FDA. An analytical laboratory that provides analytical data for toxicological studies that will be submitted to the FDA must manage its facility, procedures, and personnel in compliance with GLP regulations. The BDP contracts and/or provides products to selected analytical laboratories to conduct GLP testing and provides oversight to confirm that this testing is conducted in compliance with GLP requirements.

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

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appropriate, as per ***SOP 21900 - Expectations for the Production of Product for Toxicology Testing***.

9.1.1 21 CFR **58.35 Quality assurance unit.**

(a) A testing facility shall have a quality assurance unit which shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

(b) The quality assurance unit shall:

(1) …

(4) Periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken.

(5) Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation.

(6) …

(c) The responsibilities and procedures applicable to the quality assurance unit, the records maintained by the quality assurance unit, and the method of indexing such records shall be in writing and shall be maintained.

9.2 **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).

9.2.1 **21 CFR 211.22 Responsibilities of quality control unit.**

(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.

(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.

(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.

(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.

9.3 **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.

9.4 **21 CFR 610, General Biological Products Standards –** The regulations in 21 CFR 610 contain the minimum current requirements or general biological product standards including requirements for product release; potency, safety and sterility testing; standard preparation; mycoplasma testing; hepatitis controls; dating periods and labeling 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.

10.0 References and Related Documents

10.1 **SOP 21900 –** ***Expectations for the Production of Product for Toxicology Testing***

10.2 21 CFR 211.22, Responsibilities of Quality Control Unit

10.3 21 CFR 211.100, Written Procedures

10.4 21 CFR 211.160, Laboratory Controls

10.5 21 CFR 58, Good Laboratory Practices

10.6 21 CFR 600, Biological Products: General

10.7 21 CFR 610, General Biological Products Standards

11.0 Attachments

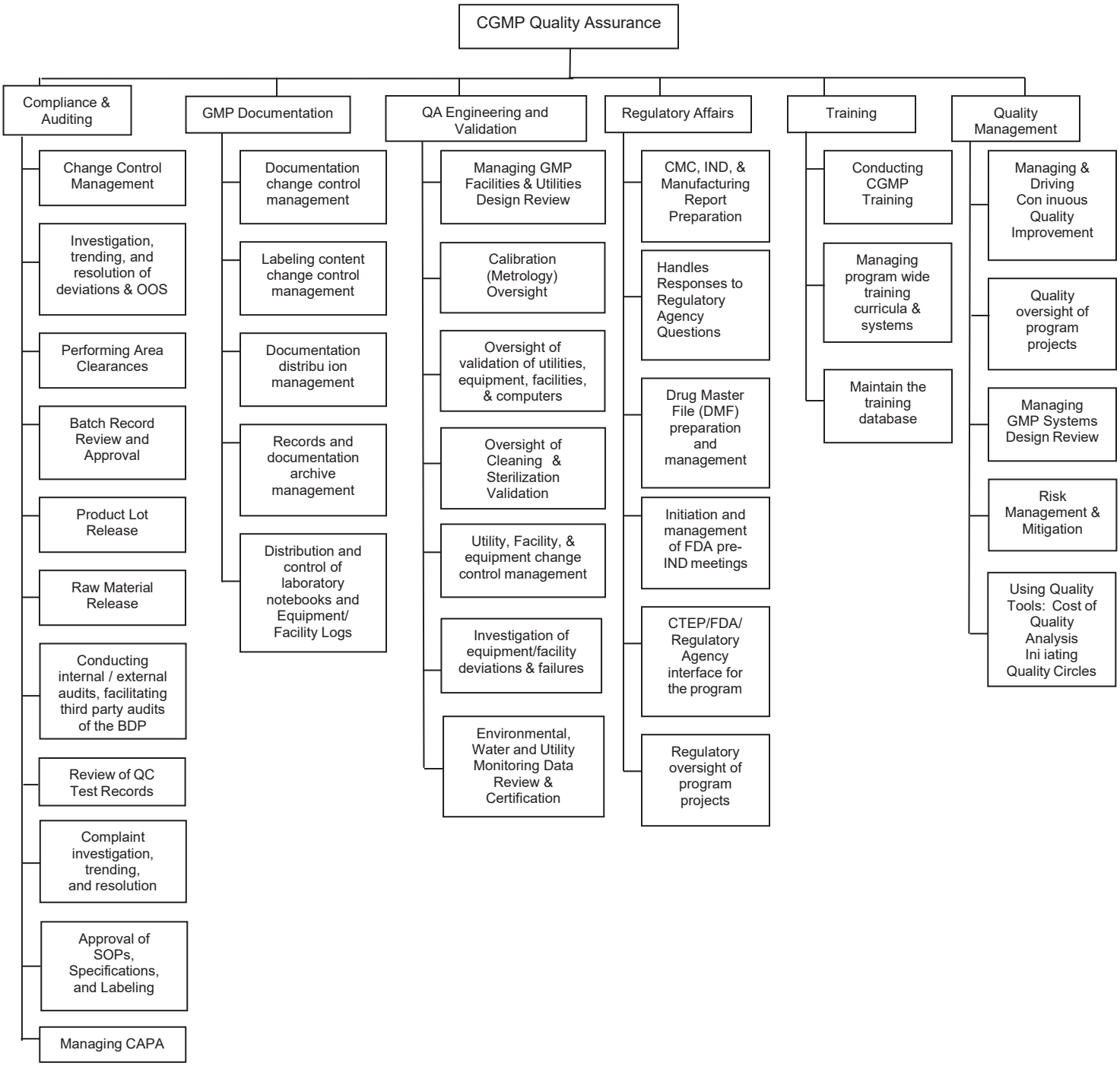
11.1 **Attachment 1** Quality Assurance - BQA Functional Organization Chart

11.2 **Attachment 2** BQA SOP List

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

Attachment 1

Quality Assurance – BQA Functional Organization Chart



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Attachment 2

BQA SOP List

SOP Number	SOP Title
	Auditing and Compliance
21001	Policy for Visitors to the GMP Facilities
21002	Product Release
21004	Administration and Configuration of TrackWise Software
21006	Quality Assurance Operations, Responsibilities, and Authority
21008	BDP Material Review Board
21101	Internal CGMP Compliance Auditing
21103	Quality Assurance Review of Completed Batch Production Records and Other Manufacturing Production Records
21104	Pre-Production Clearance
21105	Conducting External Audits
21106	Certificate of Origin Policy for Raw Materials/Components Used at the BDP
21107	Review of Process Analytic Test Records by Quality Assurance
21108	Establishing a BDP Quality Agreement with Subcontractors
21109	Supplier Qualification Program
21301	Deviations from Written Documents and Corrective and Preventative Actions
21409	Good Documentation Practices
21411	Printing, Inspection, and Reconciliation of Product Labels
21600	Training and Qualification of Personnel in a CGMP Environment
21603	Using the PLM Administrator Module
21701	Management of Sponsor Audits
21702	Policy and Operational Procedure for Contract Manufacturing by the BDP
21704	Biopharmaceutical Quality Assurance Hold/Quarantine Policy for Materials and Product
21705	Request for Additional Processing of Drug Substance or Final Drug Product
21706	Personnel Health Restrictions in Product-Contact Environments
21707	Deposit/Withdrawal of Product and Samples in the NCI-Frederick Repository
21708	QA Disposition of CGMP Raw Materials
21709	Handling and Storage of CGMP Mammalian, Bacterial, and Viral Bank Materials
21710	TrackWise Configuration Migrator Application
21900	Expectations for the Production of Product for Toxicology Testing
21902	Requirements for Establishing Part Numbers and Specifications for BDP Components and Materials
21903	Using the Part Number/Master Specification Program to Establish Raw Material Part Numbers and Master Specifications
21904	Consultants to the BDP
21906	Destruction of BDP-Produced Materials
21908	Establishing Quality Agreements with Contract Testing Organizations
21909	Cell Therapy Product Release
21910	Integrity of BDP Data
21911	Quality Assurance Record Review for Cell Therapy
21912	Communications Plan Cell Therapy
21913	Origination, Modification and Control of Labels for Cell Therapy

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

Attachment 2 (Continued)

BQA SOP List

SOP Number	SOP Title
	Document Control
21007	Alternate Signature Authority
21400	Format, Content, and Identification of Standard Operating Procedures
21402	Document Storage and Archival Process
21403	Origination, Modification, and Control of Labeling for GMP and GLP Products
21404	Abbreviations Used in the Biopharmaceutical Development Program
21405	Assigning and Requesting Lot Numbers for Product
21406	Personnel Signature and Initial Verification System
21407	Records Retention
21408	Laboratory Notebooks Control and Use
21410	Management of Project-Related Documentation
21413	Processing of Approved Standard Operating Procedures
21415	Preparation and Approval of Master Production Records
21416	Creation and Use of Electronic Copies of GMP Documents
21417	Distribution of Documents to External Recipients
21418	Control and Request of Documents/Records
21419	Origination, Modification, and Approval of Documents
21420	BQA Clearance of Employees Terminating Employment from the BOP
21421	Confidentiality and Security of BOP Information and Documents
21905	Processing of Approved Electronic IBC Submissions into the IBC Database
	Engineering and Validation
21500	General Policies and Procedures for Balances
21503	Responding to Alarms
21505	Testing of In-Line Conductivity Meters
21506	Calibration of Pressure-Measuring Devices
21507	Monitoring Temperature with Chart Recorders
21508	Equipment Calibration Program
21541	Calibration of Temperature-Measuring Devices
21520	Equipment Management and Control
21523	Calibration Data Review
21525	Responding to Power Outages in Building and I of the -
21526	Engineering Event Management
21529	Equipment Interproduct Cleaning and Clearance
21531	Equipment Logs
21533	Policies for Operation, Cleaning, and Routine Maintenance of Controlled Temperature Equipment
21536	Calibration of Differential Pressure Gauges
21539	Cleaning Verification Swab Sampling
21541	Use of the Kaye Validator® System for Qualification or Other Data Acquisition Studies
21548	Veriteq vLogReader Data Downloading and Graphing System
21553	Guidance for Return-to-Service Activities for Utility Systems and GMP Areas

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Attachment 2 (Continued)

BQA SOP List

21554	GMP Area Status Management
21555	Use and Management of Blue Mountain Regulatory Asset Manager
21556	Certification and Replacement of HEPA/ULPA Filters by Contractors or FME
21558	Guidelines for using Temperature Recording Devices for Validation
21907	Access Control for BDP Areas of the ATRF
	Regulatory Affairs
24101	Field Withdrawal or Correction of Investigational Products
24200	Protection of Personally Identifiable and Health Information
24300	Communication with Regulatory Agencies
24301	Inspections by Regulatory Agencies
24302	Establishment and Use of an FDA Electronic Submissions Gateway (ESG) Account
24401	Preparation of Pre-IND (Type B) Meeting Request Letters
24404	Content of an Investigational New Drug Application (IND)
24405	Preparing a Meeting Information Package for a Pre-IND (Type B) Meeting
24406	Preparation of the CMC Portion of Pre-IND Read Ahead Packages
24407	Preparation of Manufacturing Reports
24408	Preparation of Regulatory Documents
24410	Preparation of Amendments to a Type V Facilities Electronic Drug Master File (CBER Format)
24411	Preparation of a Chemistry, Manufacturing, and Controls Section in Common Technical Document (CTD) Format

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