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1.0 Purpose

This Standard Operating Procedure (SOP) describes the procedure for the control and request of documents/records in the Biopharmaceutical Development Program (BDP).

2.0 Scope

This SOP applies to BDP departments involved in controlling or requesting CGMP documentation (SOPs, Master Production Records (MPRs), Master Specifications (MSs), Certificates of Analysis (COAs), Technical Documents, Protocols, etc.), as well as other documentation regulated by federal, state, and/or local statute.

This SOP does not apply to the origination, modification, or approval of documents (See ***SOP 21419 - Origination, Modification and Approval of Documents***).

This SOP does not apply to submissions generated by Regulatory Affairs for regulatory agencies or to origination, modification, and control of labeling. (See ***SOP 21403 - Origination, Modification, and Control of Labeling for GMP and GLP Products and 21913 - Origination, Modification and Control of Labels for Cell Therapy.***)

3.0 Overview

Documents controlled by BDP are controlled through their document number, revision level and effective date. Changes to documents are controlled using a change control mechanism. This change control mechanism is either through an electronic Document Management System (eDMS) or using an electronic Document Change Record (DCR) and a change justification form.

4.0 Authority and Responsibility

4.1 The Director, Regulatory Compliance has the authority to define this procedure.

4.2 BDP employees are responsible for updating a controlled document when it is no longer accurate, is obsolete, or needs to be updated for any reason.

4.3 BQAD (or designee) is responsible for:

- Assigning document numbers outside of the eDMS.
- Issuing, tracking, and controlling GMP related documents.
- Providing new or revised controlled copies of SOPs for SOP Control Copy Manuals.
- Destroying copies of obsolete GMP related documents.
- Archiving originals of obsolete GMP related documents (refer to ***SOP 21402 - Document Storage and Archival Process***).
- Updating the document tracking databases as needed.
- Maintaining electronic versions of GMP related documents.
- Checking Master Production Record (MPR) and/or Validation protocol template master file for approval signatures and dates prior to issuing the document for use.
- Signing BPR documents, as appropriate, and dating it to show that it has been checked page by page to ensure it is an accurate reproduction of the master document.
- Maintaining hard copy files for project related documentation as needed.

5.0 Control of Documents

5.1 Documents are controlled and maintained either electronically in the eDMS or through a physical copy maintained by BQAD. BQAD maintains original, current documents in the Document Control Room except for SOPs and Forms. Access to the Document Control Room is restricted and under the control of BQA. Documents are stored in the Document Control Room or in off-site storage. SOPs and forms are maintained the Master Control eDMS and are available for electronic review and downloads.

5.2 Electronic versions (PDF format) of some documents are available on BDP's network public directory (such as completed BPRs, part number requests, master specifications, stability documents, and on-line forms). The electronic versions of GMP related documents are maintained by BQAD. SOPs and forms are maintained and updated in the Master Control eDMS.

5.3 If extensive revisions were made to a document, the electronic redlined copy of the last draft of the document before final approval is maintained by BQAD as an addition to the revision page. Redlines and versions of all documents are maintained in MasterControl in the collaboration workspace.

5.4 A master file is maintained for each official, signed, and approved document. Prior to the implementation of an eDMS a physical file was maintained for all documents. With the implementation of the eDMS the Master File is transitioned to an electronic file within the eDMS for revisions established in the eDMS.

5.4.1 The physical master file contains signed and dated originals of the document as well as the obsolete revisions. The original signed master document for a prior revision is retained in the Document Control Room (or off-site storage if needed). Refer to ***SOP 21402 - Document Storage and Archival Process***.

5.4.2 The master file of the document may also contain any comments received concerning changes or suggestions that may be needed when the document is revised. For documents controlled outside of the eDMS, any request for revision, BQAD provides an electronic copy of the document in a common electronic folder for update.

For documents controlled outside of the eDMS, a portion of the master folder is established for each document to record the chronological history of the document, including origination, revisions, holds, deletions, etc. The historical account for the document is usually the revision summary.

6.0 Document Numbers

6.1 Documents are controlled by their identification numbers. For any document controlled by the eDMS, the system is configured to assign the numbers.

6.1.1 SOPs and associated forms are numbered per ***SOP 21400 - Format, Content and Identification of Standard Operating Procedures***.

6.1.2 MPR identification numbers are assigned per ***SOP 21415 - Preparation and Approval of Master Production Records.***

6.1.3 Stability Protocol identification numbers are assigned in sequential order, e.g., SP-001, SP-002.

6.1.4 Parts Replacement Schedule identification numbers are for a piece of equipment that is to be replaced during the changeover process in sequential order, e.g., PRS-01, PRS-02.

6.1.5 Certificate of Analysis and Master Specifications (COA, MS) identification numbers are given in sequential order. COA designation is first, the project number associated next, and then the sequential number. MS numbers are given in the same format, e.g., COA-0510-02, MS-0474-01.

6.1.6 For projects that have the same COA template used for multiple lots, a COA template may be used. The numbering for these documents is COA-0598-T01-01. The T01 is the template number.

6.1.7 Sampling schedules (SS) are given sequential identification numbers. The SS designation is first, then the year the sampling schedule number was given, then the sequential number, e.g., SS-18-001, SS-18-002.

7.0 Revisions of Documents

7.1 The original approved document begins at a revision level of 00. Subsequent, approved documents increase in revision level in increments of 1.

7.2 For the eDMS the version level of the document increases each time the draft infocard is saved or updated. Revisions and Versions and the document history in the eDMS are available through the document infocard.

8.0 Document Control Record

8.1.1 The document control record is used as a mechanism to control the review and approval of the document.

8.1.2 For documents controlled by eDMS, the task packet is defined in the system configuration and may be specific to a document type. The task packet includes the DCR number (DCR-YYYY-NNN), a summary of changes and reasons for change as well as any custom fields defined to communicate requirements to the approvers and BQAD.

8.1.2.1 A Document Control Record (DCR) Form 21419-01 is used for documents controlled outside of the eDMS. The form is completed electronically by the document author and the justification for changes before a draft is created.

8.1.2.2 BQAD assigns a tracking number through the electronic tracking system used. The numbering format for these DCR numbers is (YYMMDDNNN). BQAD assigns a tracking number and completes a DCR to be routed as a separate file with the document to be approved. A revision justification form completed for revised documents and is routed with the document. Once all signatures are obtained, BQAD logs the DCR back into the routing database and marks it complete. The completed DCR forms are kept in the folder with the original document.

8.1.3 It is recommended that initiators of new documents attach supporting documentation to the DCR or the task packet that justifies the creation of the document including an explanation/justification for:

- Selected tests, specifications, ranges, and limits
- Type and grade of specified raw materials
- Specified processes or procedures
- Other specifications

9.0 Effective Dates

Effective dates for eDMS are assigned by the author based on the need for the updated document. Non-eDMS documents are considered effective on the date of the last approval signature.

10.0 Obsolete Documents

10.1 BQAD or the eDMS will obsolete the previous revisions on the effective date approved document.

10.2 If a new document is assigned a different numbering series, the original document number assigned becomes obsolete. This information is noted in the database system for cross referencing purposes.

10.3 Obsolescing a document in the eDMS follows the same process as does the review and approval. See ***SOP 21010 User Manual for MasterControl.***

10.4 When obsolescing a document outside of the eDMS a request is submitted to BQAD through the BQAD Outlook Mailbox to obsolete a document. The following steps are taken:

10.4.1 The requestor provides a justification to obsolete the document. The email including the justification is printed and included in the document master file in the Document Control Room.

10.4.2 BQAD confirms the request with the author of the document if they are not the requester for obsoleting the document, and the appropriate BQA Manager.

10.4.3 Once approval is obtained, BQAD updates its status to “obsolete” in any databases for the document and adds the date BQA approved the document to be obsoleted.

10.4.4 An approval to obsolete a document shall result in the recall and destruction of hard copies in official circulation (Control Copies). The master hard copy document is stamped OBSOLETE, dated, and initialed, and kept in the BQA files.

10.4.5 Obsoleted documents that are available electronically on the BDP Public network should be relocated if no longer needed or replaced with a current version of the document.

10.5 Once a document has been issued a number, that number can never be used again. The signed masters of obsoleted and deleted documents are stored in the BDP QA Document Control Room or at an off-site archival location.

NOTE: Obsoleted documents that are controlled in the eDMS are stored in the eDMS.

11.0 Document Storage

11.1 Recently completed and active documents are maintained in the BDP QA Document Control Room or archived at an off-site facility.

11.2 It is the responsibility of the department submitting documents to be archived to submit a list of documents to be archived that includes, but is not limited to, the titles of the documents, any document numbers (BPR numbers, equipment logbook numbers, Laboratory Notebook numbers, etc.), names of people associated with the documents, and document dates with a completed Form 21402-01, Archive Request to BQAD. See ***SOP 21402 - Document Storage and Archival Process*** for the complete archive process.

12.0 Issuance of Controlled Copies

12.1 SOP manuals are customized collections of official copies of SOPs. They contain those SOPs that pertain to the operations that are conducted in the areas in which they are located. They are available to appropriate personnel and located in designated areas.

12.1.1 Each SOP Manual is assigned a unique number by BQAD.

12.1.2 The issuance and reconciliation of controlled copies is defined in ***SOP 21916 - Issuing Controlled Copies.***

12.1.3 Copies are issued to manual owners who acknowledge the receipt of a controlled copy and return any previous revisions.

12.1.4 Each manual owner is responsible for the upkeep of their SOP manual with copies issued by BQAD.

12.1.5 BQAD reconciles a sampling of SOP Manuals annually.

12.2 MPRs and BPRs

12.2.1 MPRs are distributed by BQAD as soon as possible upon receipt of the e-mail request and date needed. Refer to ***SOP 21415 - Preparation and Approval of Master Production Records***. An MPR is a document that can be requested for revisions or used as a template for a similar MPR. Once it is printed, has a lot number affixed, and has information recorded on it, then it is known as a Batch Production Record (BPR).

12.2.2 BPRs may be requested on Form 21405-01, Request for Lot Number/Batch Production Record per ***SOP 21405 - Assigning and Requesting Lot Numbers for Products***, when the lot number is assigned or can be requested from BQAD by e-mailing the BQAD Outlook Mailbox at a later date. The e-mail must include the MPR number, project number, and if it is cGMP or cGLP. Batch records are issued per ***SOP 21923 Control and Issuance of Batch Production Records for Use in Manufacturing***

12.2.3 Only approved and effective MPRs are issued for use as BPRs for cGMP production activities by BQAD. BPRs for GLP use may be issued as draft documents by BQAD for production use.

12.2.4 To issue a BPR, BQAD (or designee) needs to enter the lot number, project number, and, into the electronic version of the MPR and print the document.

12.3 Validation Protocols

12.3.1 Validation protocols are requested for execution by e-mail to the BQAD Outlook Mailbox. The e-mail should include the protocol number being requested, and when applicable, the MEF ID and name of the equipment or system to be validated, and the building/room number where the equipment or system is located. Protocols are distributed within two weeks of receipt of the request, if possible.

12.3.2 Issuing a templated validation protocol for execution:

12.3.2.1 Validation templates are documents that have already been approved with signatures and dates. Validation templates exist for the following, but are not limited to:

- Controlled Temperature Storage Equipment
- Controlled Rate Freezers
- Autoclaves
- Incubators
- Purified Water Generation Systems
- Bioreactors/Fermenters
- Emergency Power Generator Systems

12.3.2.2 The master file is checked for approval signatures and dates upon receiving requests for templates, protocols, etc. No document is issued for use/execution unless approval signatures and dates are in place.

12.3.2.3 In issuing the validation protocol, the following information is entered into the header of the document and saved the document with a new file name:

- The unique protocol number
- The effective date
- The location of the equipment or system.
- The MEF number and equipment or system name, if applicable

12.3.3 Issuing specific validation protocols (i.e., equipment, process, or software protocols) for execution:

12.3.3.1 A copy is made of the approved protocol and BQAD provides a hard copy of the protocol to the person(s) responsible for protocol execution. The document is then executed and returned to BQAD (or designee) for review and final approval signatures. The completed BQA reviewed and approved protocol is filed in the Document Control Room.

12.4 External Requests for Documents

A Document Distribution Form, 21417-01, is required for each external request for documents (outside Leidos Biomedical Research, Inc., or NCI-BRB) (see ***SOP 21417 - Distribution of Documents to External Recipients***)

13.0 Return of Documents

13.1 Termination of Employment

13.1.1 When an employee terminates employment, controlled documents in the employee's possession must be returned to BQAD before the employee's last day of employment. Alternatively, they can be transferred to the manager or a person that will be replacing the individual if work is to continue in said controlled documents. Examples of these documents are laboratory notebooks, equipment logbooks, project file notes, SOP Manuals, etc.

13.1.2 BQAD must be notified of any documents transferred or reassigned to another person. See ***SOP 21420 - BQA Clearance of Employees Terminating Employment from the BDP*** for complete details of the process followed by BQAD (or designee) when an employee terminates employment.

13.2 BPR Issued but Not Used

If a BPR is issued but not used (No data collected or entered in the BPR), it should be returned to BQAD for filing with the appropriate project files and reconciled in the MEF database.

13.3 Validation Protocol Issued but Not Used

13.3.1 A request can be sent to BQAD to mark an issued non-executed validation protocol as "unexecuted.". A non-executed validation protocol is defined as No data collected/entered in the validation protocol.

13.3.2 Upon request (by e-mail from the Validation Manager) "to Mark XYZ document as unexecuted", BQAD, prints the requested email message, which includes the justification for change of status and file the email request in the original hard copy validation protocol folder.

13.3.3 BQAD updates the Validation Protocol database, noting the paper executable validation protocol has been destroyed stating the requestor's name and date of the request.

NOTE: No electronic documentation is deleted.

14.0 SOPs Posted on the BDP Website

14.1 Any SOP posted to the BDP website must be approved by the NCI/BRB prior to posting. The Website is updated quarterly with any new or revised SOPs.

14.2 SOP titles are posted on the BDP website. SOPs and other documents listed on the on website may be requested for reference use only.

14.3 SOPs and other documents available via the BDP website must have any proprietary information redacted by BQAD. Supplied SOPs must clearly state that they are uncontrolled copies to be used for training and reference purposes only. Documents requested through the BDP website are required to be made 508 Compliant.

14.4 BQAD redacts new or revised SOPs and submits them to Data Management System (DMS) to be placed on the BDP website server to be automatically e-mailed to the individual who requested the document via the BDP Website.

14.4.1 The following items should be redacted from SOPs to posted on the website:

- Revision pages
- Project Specific Information
- Signatures (for any documents issued outside of Master Control eDMS)
- Building Numbers / Room Numbers

14.5 SOPs posted on the BDP website are flagged in Master Control as a Custom Field.

14.6 DMS removes any SOPs that have been made obsolete from the website at the request of the BDP.

15.0 Acronyms and Definitions

15.1 **BQA –** Biopharmaceutical Quality Assurance

15.2 **BQAD –** Biopharmaceutical Quality Assurance Documentation

15.3 **COA –** Certificate of Analysis

15.4 **DCR –** Document Control Record.

15.5 **DMS** - Computer & Statistical Services, **Data Management Services**, Inc., Contractor

15.6 **MS –** Master Specification (previously known as AP- Assay Profile)

15.7 **Approve –** A review disposition of approve indicates that the reviewer accepts the document, and the proposed changes as is. In the case of an obsolete document, approval indicates agreement to obsolete the document.

15.8 **Approved Document –** A document that has been signed and dated by the author, at least one Supervisor or management person knowledgeable and relevant to the document, and BQA.

15.9 **Batch Production Record (BPR) –** A copy of a Master Production Record that has had a lot number assigned to it and is used to record manufacturing-related data.

15.10 **Document –** A written or printed on paper or electronic image bearing the original, official, or legal form of information that can be used to communicate decisive information or proof.

15.11 **Effective Date –** The effective date of documents, other than SOPs, is the date of the last approval signature. The effective date for SOPs is fourteen (14) calendar days after the last approval date, immediately, or a custom date. This is to allow time to conduct training.

15.12 **GMP Controlled Document –** A document that has been created to comply with CGMP regulations. This includes, but is not limited to, Master Production Records, Master Specifications, Standard Operating Procedures, Validation Protocols, Stability Protocols, Technical Reports, and Certificates of Analysis.

15.13 **Master Production Record (MPR) –** A document that lists the manufacturing specifications and procedures, or references to such, to produce regulated products. This is the master blank manufacturing document that is later issued for a specific lot and becomes a Batch Production Record.

15.14 **Obsolete Document –** A document that had been approved and effective that is no longer required for use or has been superseded by a newer version.

15.15 **Redline –** Process of marking up a document (either hard copy or electronic) to indicate proposed changes.

15.16 **Reject –** A reject disposition indicates that the document is not acceptable as written and is not to be revised. The review process stops. The document can be resubmitted under a new tracking number.

15.17 **Revise –** A review disposition of revise indicates the reviewer will accept the document only with additional changes as noted.

15.18 **Standard Operating Procedure (SOP) –** An approved document that describes a policy, system, routine operation, such as a technical procedure, use of equipment, validation and calibration procedures, or document preparation.

15.19 **Technical Document (TD) and Master Plans (AMP- Analytical Validation Plan/VMP-Validation Master Plan) –** A technical document describes the rationale, analysis, or science associated with a procedure used to provide data and information to support the use or testing of GMP equipment, systems, processes, product, or regulatory submissions.

15.20 **Validation Protocol (VP) and Revalidation Protocol (RV) –** A formal, written approved plan for conducting a validation study. Protocols are used for installation, operation and performance qualifications, and process validations. Validation Final Reports list the outcome of a completed validation study including any operational limitations that were identified.

16.0 References and Related Documents

- **SOP 15107** *Request for Reagent Solutions*
- **SOP 21010** *User Manual for Master Control*
- **SOP 21400** *Format, Content, and Identification of Standard Operating Procedures*
- **SOP 21402** *Document Storage and Archival Process*
- **SOP 21403** *Origination, Modification, and Control of Labeling for GMP and GLP Products*
- **SOP 21404** *Abbreviations Used in the Biopharmaceutical Development Program*
- **SOP 21405** *Assigning and Requesting Lot Numbers for Products*
- **SOP 21415** *Preparation and Approval of Master Production Records*

- **SOP 21417** *Distribution of Documents to External Recipients*
- **SOP 21419** *Origination, Modification, and Approval of Documents*
- **SOP 21420** *BQA Clearance of Employees Terminating Employment from the BDP*
- **SOP 21600** *Training and Qualification of Personnel in a CGMP Environment*
- **SOP 21913** *Origination, Modification, and Control of Labels for Cell Therapy*
- **SOP 21916** *Issuing Controlled Copies*
- **SOP 21923** *Control and Issuance of Batch Production Records for Use in Manufacturing*