Frederick National Laboratory for Cancer Research, Frederick, MD

Biopharmaceutical Development Program

Standard Operating Procedure

Title: Origination, Modification, and Approval of Documents

SOP Number: 21419

Revision Number: 05

Supersedes: Revision 04

Effective Date: SEP 03 2020

Originator/Date: [redacted]

Approval/Date:

Approval/Date:

Table of Contents

1.0 Purpose

This SOP describes the procedure for the origination, revision, and approval of documents / records in the Biopharmaceutical Development Program (BDP).

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

2.0 Scope

This SOP applies to BDP departments involved in initiating and revising CGMP documentation (Standard Operating Procedures, Master Production Records, Certificates of Analysis, Master Specifications, Technical Documents, Protocols, et cetera.), as well as other documentation regulated by federal, state, and/or local statute.

This SOP does not describe controlling or requesting documents (Refer to ***SOP 21418 - Control and Request of Documents/Records***). It also does not apply to submissions generated by Regulatory Affairs for regulatory agencies. This procedure does not apply to origination, modification, and control of labeling. (Refer to ***SOP 21403 - Origination, Modification, and Control of Labeling for GMP and GLP Products***).

3.0 Authority and Responsibility

3.1 The Director, Biopharmaceutical Quality Assurance (BQA) has the authority to define this procedure.

3.2 It is the responsibility of each BDP department to prepare the content of documents, which are pertinent to its respective functions following the guidance in this SOP.

3.3 BDP employees are responsible for alerting their Supervisors and/or BQA (by emailing the BQAD Outlook mail-box) whenever a controlled document is no longer accurate, is obsolete, or needs to be updated for any reason.

3.4 BQA (or designee) is responsible for:

- Formatting, issuing, tracking, and controlling documents. (Refer to ***SOP 21418 - Control and Request of Documents/Records***.)
- Destroying copies of obsolete or deleted documents. (Refer to ***SOP 21418 - Control and Request of Documents/Records***.)
- Archiving originals of obsolete or deleted documents. (Refer to ***SOP 21402 - Document Storage and Archival Process***.)
- Notifying BDP personnel when new or revised documents are effective.
- Updating the document-tracking database.
- Reviewing every document for the following
    - Approval signatures and dates.
    - Correct effective date and revision number.
- Checking the Master Production Record (MPR) and/or Validation Protocol template master file for approval signatures and dates prior to issuing the document for use.
- Signing the document, as appropriate, and dating it to show that each page has been checked, page by page, to ensure it is an accurate reproduction of the master document (e.g., batch production records).

3.5 It is the responsibility of Supervisors/Managers to train their personnel on new and revised documents that pertain to their operations and to send documentation of training to the BQA Manager. (Refer to ***SOP 21600 - Training and Qualification of Personnel in a CGMP Environment***).

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

3.6 BQA is responsible for quality oversight of this procedure.

4.0 Origination and Processing of New Documents

4.1 Supervisors and other management personnel are required to prepare and maintain appropriate and current documents for their functional areas. The preparation of documents may be delegated to knowledgeable co-workers, subordinates, or consultants.

4.2 Personnel are to request an original document number from BQA for each new document to be written. This request should be made by email to the BQAD Outlook mail-box and be specific about the document version being requested. BQA (or designee) assigns the document number and maintains tracking databases containing relevant information for each document type.

4.2.1 SOP identification numbers are assigned per ***SOP 21400 - Format, Content, and Identification of Standard Operating Procedures***.

4.2.1.1 See Attachment 1 for the lifecycle flow of an SOP from creation to when the document becomes obsolete.

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

4.2.3 Stability Protocol identification numbers are given by BQA (or designee) in sequential order, e.g., SP-001, SP-002, et cetera.

4.2.4 Parts Replacement Schedule identification numbers are assigned by BQAE or designee (for a piece of equipment that is to be replaced during the changeover process) in sequential order, e.g., PRS-01, PRS-02, et cetera.

4.2.5 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, et cetera.

4.2.6 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, et cetera.

4.2.7 Validation protocols are given identification numbers in one of the ways listed below:

4.2.7.1 There are <u>templates</u>, which do not require approval for issuance of each individual protocol. These may be used for equipment types where there are multiple units or for protocols repeated routinely for revalidation. Equipment that typically utilize validation templates include, but are not limited to, controlled temperature storage units, incubators, water purifiers, bioreactor skids, and emergency power. If a protocol template is requested, the template is used, and it is assigned the next sequential number for that protocol type, e.g., IOQ-0142. The unique Equipment Identification Number (MEF) and Title of the protocol are entered in the document header.

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

4.2.7.2 If there is no template for the equipment requiring validation, then a document is written and submitted to BQA (or designee) for processing. The protocol is given the next sequential number for the specific validation (IOQ, PQ, PV, et cetera) and approved before the field copy for execution is issued.

4.2.7.3 A **revalidation** is the process of providing documented evidence that a utility, piece of equipment, or process has been maintained in a validated state since the last validation work was completed. Revalidation occurs because of a change-based (Engineering Event) or time-based assessment. Revalidations are given their own unique number with a suffix attached (RV), e.g., IOQRV-241, or PQRV-241).

4.3 A Document Control Record (DCR) Form 21419-01 (refer to Attachment 2) needs to be completed for new SOPs, MPRs, COAs, Master Specifications, Validation Protocols, and Stability Protocols. The form should be filled out electronically by the document author and the justification for the new document approved before it is created.

4.3.1 The purpose of the document that the DCR form applies to should be described in the middle section of the DCR under “Record the purpose for this DCR”. For new documents, fully explain/justify why it is needed. It is recommended that initiators of new documents attach supporting documentation to the DCR 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

4.3.2 The following areas of the DCR are completed by the requestor/initiator of the new document:

4.3.2.1 Requestor

4.3.2.2 The date the DCR is initiated.

4.3.2.3 Title/Description of the document.

4.3.2.4 Revision number: N/A

4.3.2.5 Select the type of document being routed by placing a check mark beside the appropriate document or add the type in the blank for “other”.

4.3.2.6 Select the function of the DCR: “new”.

4.3.2.7 Note the reason the document is being routed (i.e., refer to Section 4.3.1 above).

4.3.2.8 List the names of the individuals needed to approve the document request including a Quality Assurance Manager or Director.

4.3.3 Forward the DCR to BQA via an email to the BQAD Outlook Mailbox.

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

4.3.4 The following areas of the DCR are completed by BQAD for new documents:

4.3.4.1 The document number (i.e., SOP number, MPR number) will be assigned by BQAD and added to the DCR.

4.3.4.2 BQA will assign a Tracking number (as assigned by the Routing Feature of the SOP/MEF Database).

4.3.5 BQAD will then electronically route the DCR request for a new document to the approvers.

4.3.6 Approved original DCRs are kept with the document and a copy is included (as a separate file) with the new document for review and approval, so reviewers know the document has been approved to move forward.

4.3.6.1 If the DCR "Reject" designation is made by any reviewer, the DCR cycle is terminated and the requester is notified that new document was rejected. A new DCR is required to re-initiate a new document. The original DCR with the rejection is returned to BQA to file.

4.4 If an existing document is going to be used as a template for a new document, a request should be emailed to the BQAD Outlook mailbox. A request should be made for the template at least **10 business days** in advance of when the document is needed.

4.5 SOPs and MPRs shall be written so that any individual versed in the general knowledge to which it applies understands and can effectively perform the instructions in the document.

4.6 Documents shall be prepared in standard format per the respective document type. BQA (or designee) can provide the correct format for a document or assist authors with formatting their documents appropriately.

4.7 Once the document is drafted, notify BQA via the BQAD Outlook Mailbox. When using an existing document as a template, the requestor makes the necessary changes using the "Track Changes" feature in Microsoft Word.

4.8 BQA formats the document with necessary changes, as appropriate. Any questions or discrepancies are resolved with the originator in coordination with BQA (or designee). See Section 6.0 for Review and Approval of Documents.)

5.0 Modification of an Existing, Approved Document

5.1 To revise a document (other than an SOP) that has been issued, an email request is sent to the BQAD Outlook Mailbox. Requests for revisions are required at least ten working days in advance of when the final document is needed, if possible.

SOP revisions must be requested through the SOP/MEF database by clicking on the "Request Draft" button, which starts the automated system for initiating/tracking SOP revisions.

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

5.2 A link to the folder location with a copy of the document to be revised along with a Revision/Justification Form 21419-02 (see Attachment 3) is sent to the requestor via e-mail. The Revision/Justification form should be completed as follows:

5.2.1 Fill in the item number (1, 2, 3…), the section number that changed, the revision, and the reasons for revision with the justification for each change on the Revision/Justification, Form 21419-02 that is provided by BQA (refer to Attachment 3). Describe the probable product impact, if any under the justification for the revision section.

5.2.2 Describe each proposed change in sufficient detail to allow a knowledgeable person who is not involved with the proposed change to understand the various aspects and considerations of the change including the areas, products, and parts of the quality system that may be impacted by the changes.

5.2.3 Carefully and completely explain why the change is necessary.

5.3 Once the revised document and revision form are completed an email is sent by the author to the BQAD Outlook Mailbox to notify BQA that the document is ready for review. Once BQA (or designee) has properly formatted the document, it is routed for review and approval (refer to Section 6.0).

5.4 Once the revised document has been approved, the previous version will become obsolete. Refer to ***SOP 21418 - Control and Request of Documents/Records*** for the steps taken for obsolete documents.

6.0 Review and Approval of Documents

6.1 Once a document is ready for review, BQA (or designee) tracks the document review process (unless instructed otherwise) and provides a link to the location of the document and Revision/Justification form via e-mail to each reviewer. Refer to Attachment 1 for a flow chart of the overall SOP Process.

6.1.1 Simultaneous Review

The document is placed in an online review folder with the Track Changes feature enabled. Each reviewer can see the suggested changes proposed by other reviewers and enter any questions and comments they may have into the online document. The reviewers will redline the document and make suggestions for corrections and/or changes, as appropriate (electronically) in Microsoft Word using Track Changes. If a reviewer has suggestions for major changes, the reviewer should consult with the originator of the document. A meeting can be called with all reviewers to address changes if necessary. Each reviewer can decide whether to approve, revise, or reject a draft document. For a document that has been rejected, the review process stops, and the draft document becomes void.

For SOPs, once a review is completed, the reviewer records the date the review is complete in the table on the first page of the draft SOP.

6.1.2 The author of the document may place a document “On Hold” at any time during the review process. The author informs BQA (or designee) that the document is “On Hold” and is to be reconsidered later.

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

6.2 Once all the necessary changes have been made and resolved with the document author, the document is formatted for approval by electronic signature and placed in a central network location that all staff can access to approve the document. BQAD assigns a tracking number and completes a DCR to be routed as a separate file with the document to be approved. Any revision justification form completed for revised documents is also routed with the document. (If a document cannot be formatted for electronic signature the document is printed and routed for final signatures and dates via a Document Control Record (DCR) Form 21419-01) (refer to Attachment 2). If necessary, the originator may hand carry the document for signatures.

6.2.1 BQAD completes the following areas of the DCR:

6.2.1.1 Name of person requesting document

6.2.1.2 The date the DCR is completed.

6.2.1.3 Tracking number (as assigned by the Routing Feature of the SOP/MEF Database).

6.2.1.4 The document number (i.e., SOP number, MPR number).

6.2.1.5 Title/Description of the document.

6.2.1.6 Revision number.

6.2.1.7 Select “other” and add the type of document.

6.2.1.8 Select the function of the DCR (i.e., new, revision, obsolete, et cetera.) or type the reason in the blank for “other”.

6.2.1.9 Include the series or category for SOPs, section (MPR-C or MPR-F), IQ/OQ/PQ (validation) etcetera.

6.2.1.10 Note the reason/purpose the document is being routed (i.e., refer to Section 4.3.1 above). If this is a document being revised include the main reason for the revision.

6.2.1.11 List the names of the individuals the document is being routed to for approval. The last person listed can be the originator of the DCR, so the document is returned to the person that originated it.

6.2.1.12 The Document Control Record may be circulated electronically, and approvers provide an official digital signature.

6.2.2 The master documents, including Standard Operating Procedures, are printed on white paper if routing a hard copy for signature.

6.2.3 If documents are to be routed for electronic signature, then BQAD will assign the effective date (at least 10 business days from the date routed for signature) (**NOTE:** Once a document is e-signed no changes can be made to it. Therefore, the effective date needs to be added prior to signatures.)

6.2.4 Once all signatures are obtained, BQA logs the DCR back into the routing database and marks it completed. The completed DCR forms are kept in the folder with the original SOP.

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

6.3 Once approval signatures for hard copy original documents are received, BQA (or designee) updates the official document with the appropriate effective date (refer to Step 7.7) (i.e., SOPs, MPRs, Validation Protocols, and PN/MSs).

Some types of documents do not get effective dates but are considered effective once all approval signatures are received (i.e., Certificates of Analysis, Master Specification, and Project Reports).

6.4 Hard copies of effective/approved documents are kept in BQA Document Control. If the final approved SOP document is an electronic document, a copy is printed and filed in the original SOP files.

6.5 Refer to ***SOP 21418 - Control and Request of Documents/Records*** for the document control procedures used for approved documents.

7.0 Definitions, Acronyms and Abbreviations

7.1 **Approval Date -** The date of the last approval signature.

7.2 **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.

7.3 **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.

7.4 **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.

7.5 **Deleted Document -** A draft document that is removed from the system prior to approval.

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

7.7 **Effective Date -** The effective date of documents, other than SOPs, is the date of the last approval signature. The effective date for SOPs is ten (10) working days after the approval date, unless otherwise requested, to allow time for personnel training.

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

7.9 **Inactive Document -** An approved effective document can be inactivated if it is not currently being used and no use is currently anticipated. Inactive status relieves the requirement for reviews until the document is needed. Once the document is requested to be put back into an active state, it must be reviewed for accuracy prior to use.

7.10 **Insignificant Change -** Any change in spelling, format, sentence structure, or verbiage (words or short phrases) that in no way alters a GMP procedure or operation.

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

7.11 **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, which is later copied and issued for a specific lot and becomes a Batch Production Record.

7.12 **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.

7.13 **On Hold Document -** The author informs BQAD to place a draft document “On Hold” to be reconsidered later.

7.14 **Product Impact Statement -** An explanation of how proposed changes may impact the product (especially for quality, potency, purity, and safety).

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

7.16 **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.

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

7.18 **Significant Change -** Any change in the purpose, scope, procedure, and materials or methods, that in any way alters the sequence, description, results of an operation, or that may impact the identity, strength, quality, or purity of the drug product. If a significant change is made during the signature process, the document is then re-routed to the author for approval again and needs to be re-signed by all parties.

7.19 **Stability Protocol -** A formal, written approved plan for conducting product-related stability studies.

7.20 **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.

7.21 **Technical Document (TD) and Master Plans (AMP/VMP) -** 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.

7.22 **Validation Protocol (VP) and Revalidation (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.

7.23 **Void Document -** A draft document that has been entered into the BQAD system, has a document number assigned, but has either been rejected during the review cycle or a decision has been made that the document is no longer required BEFORE the approved signatures have been obtained. The Director of BQA has the authority to determine if a document is void.

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

7.24 **Abbreviations**

AMP	Analytical Master Plan
BPR	Batch Production Record
BQAD	Biopharmaceutical Quality Assurance Documentation
COA	Certificate of Analysis
DCR	Document Control Record
MPR	Master Production Record
MS	Master Specification
SOP	Standard Operating Procedure
VMP	Validation Master Plan
VP	Validation Protocol
RV	Revalidation Document

See ***SOP 21404 - Abbreviations Used in the Biopharmaceutical Development Program***, for a comprehensive list of abbreviations.

8.0 References and Related Documents

8.1 **SOP 21400** *Format, Content, and Identification of Standard Operating Procedures*

8.2 **SOP 21402** *Document Storage and Archival Process*

8.3 **SOP 21403** *Origination, Modification, and Control of Labeling for GMP and GLP Products*

8.4 **SOP 21404** *Abbreviations Used in the Biopharmaceutical Development Program*

8.5 **SOP 21415** *Preparation and Approval of Master Production Records*

8.6 **SOP 21418** *Control and Request of Documents/Records*

8.7 **SOP 21600** *Training and Qualification of Personnel in a CGMP Environment*

9.0 Attachments

9.1 **Attachment 1** SOP Flow Chart

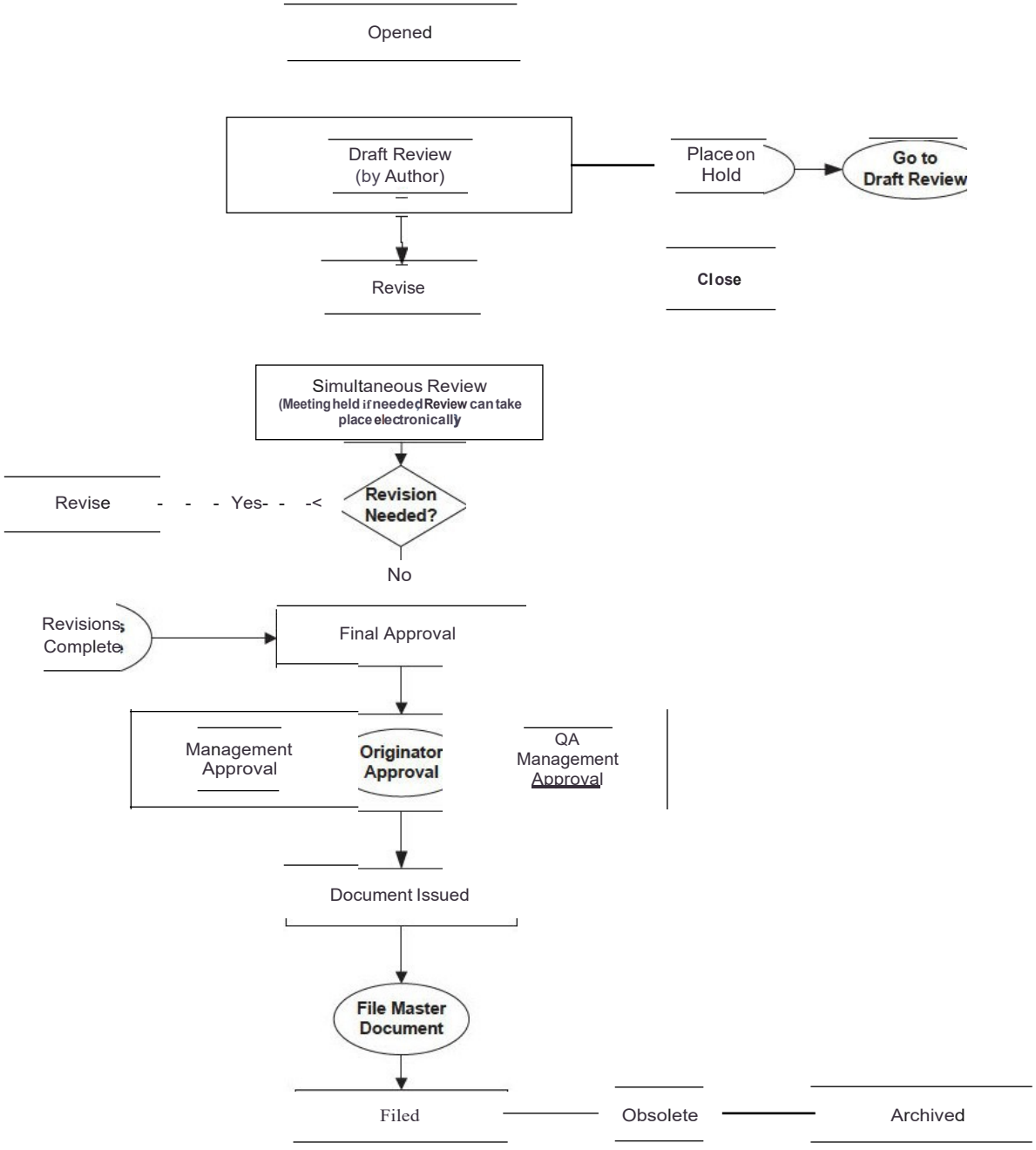
9.2 **Attachment 2** Form 21419-01, Document Control Record

9.3 **Attachment 3** Form 21419-02, Revision/Justification Form

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

Attachment 1

SOP Flow Chart



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

Attachment 2

Form 21419-01 - Document Control Record

FNLCR, BDP
Form No.: 21419-01
SOP No.: 21419
Revision 05: SEP 03 2020

Document Control Record

The requestor completes this form and sends it to NCIBDPBQAD@mail.nih.gov to initiate process

Requester	Date	Tracking Number

Document Number:	Title / Description:	New Revision Number:

Select Document Type:

☐ COA ☐ SOP ☐ Labels ☐ Stability ☐ MPR Category: ☐ VP / VR ☐ MS ☐ Other (List) ☐ Reagent Preps

Function of this DCR:

☐ New ☐ Revision ☐ Obsolete ☐ Other (List)

Record the purpose for document:

(Justification is required – If this is a new MPR, SOP, MS, COA, VP or Stability Protocol, justification for the new document should be provided and approval is required. If this is a revision to a document or another type of document other than those above, please list the purpose of this DCR and justify any changes.) Attach additional pages if necessary.

Specifics regarding changes and justifications are included on the Revision/justification Form (21419-02)

(Stop here and forward to the BQAD email box)

Document Approval

	Name	Signature/Date
☐ Accept ☐ Revise* ☐ Reject	Author:	
☐ Accept ☐ Revise* ☐ Reject	Supervisor:	
☐ Accept ☐ Revise* ☐ Reject		
☐ Accept ☐ Revise* ☐ Reject		
☐ Accept ☐ Revise* ☐ Reject		
☐ Accept ☐ Revise* ☐ Reject		
☐ Accept ☐ Revise* ☐ Reject		
☐ Accept ☐ Revise* ☐ Reject		

*Comments:

BQAD (signature/date)

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

Attachment 3

Form 21419-02 - Revision/Justification Form

FNLCR, BDP
Form No.: 21419-02
SOP No.: 21419
Revision 05: SEP 03, 2020

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Revision/Justification Form

Title:

Revision No.:

Effective Date:

Item Number	Section Changed	Revision	Justification for Revision	Add
				Remove

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