Table of Contents

1.0 Purpose

This document defines the controls to be considered for the manufacture and testing of product that will be submitted for Investigational New Drug Application (IND)-directed toxicology studies in compliance to 21 CFR 58, Good Laboratory Practices (GLP).

2.0 Scope

This SOP applies to personnel who manufacture or test products that are intended to be submitted for IND-directed toxicology studies according to 21 CFR 58, Good Laboratory Practices.

3.0 Authority and Responsibility

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

3.2 Biopharmaceutical Development Program (BDP) Managers and Supervisors have the authority and responsibility to manufacture Toxicology lots in accordance with this SOP.

3.3 BQA is responsible for quality oversight of this procedure.

4.0 Introduction

As a potential drug progresses through the research, development, and clinical manufacturing process, increasing controls are applied to protect product quality, traceability of information, and credibility of any information prepared for submission to the Food and Drug Administration (FDA). Toxicological and safety information is usually collected on the drug before it moves into the formal Good Manufacturing Practices (GMP) manufacturing phase that will produce material for clinical trials in humans.

As part of the information provided to FDA, an evaluation of clinical trial lots (GMP lots) and toxicology (Tox) lots is conducted to confirm that the GMP lots and the Tox lots are substantially equivalent and accurately represent the attributes of the new drug. This evaluation is only possible when sufficient information is collected and documented for the manufacture and testing of both GMP and Tox lots. Internal policies for the production of Tox lots help to assure that sufficient information on the manufacturing and testing process is documented.

There are few specific regulations that must be applied for the manufacture of GLP/Tox product (See 21 CFR 58.105 & 107). However, Good Laboratory Practice Regulations (21 CFR 58) primarily present the requirements for the control and execution of animal safety testing. 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. Additionally, the BDP has developed policies based on knowledge and experience to assure an appropriate degree of control in the manufacture of Tox lots.

5.0 Definitions

5.1 Tox Lot/Material/Product: Drug produced for safety/Toxicology testing (test article) that will be conducted according to the Good Laboratory Practice (GLP) Regulation (21 CFR 58). This is also referred to as a "GLP lot" or "GLP material".

5.2 Master Production Record (MPR): The master document containing detailed instructions for performance of a specific procedure. The document is used to record critical steps, parameters, raw data, etc., as events occur during the production of a product.

5.3 Batch Production Record (BPR): A copy of the MPR to which a lot number has been printed that is used to directly capture manufacturing data and any supporting testing data or documentation required to complete the batch production record.

5.4 Lab Notebook: Legal Documents that provide a mechanism to capture critical information about experiments or processes that may be needed to reconstruct events at a later time (for example, as part of a Chemistry, Manufacturing and Controls section in an Investigational New Drug Application), to serve as a foundation for future work, to transfer information from development to other departments or institutions, or to protect intellectual property.

6.0 Expectations for the Production of Tox Product

6.1 Organization and Personnel

6.1.1 Personnel must be qualified to produce Tox products. This will be evaluated based on the person's education, experience (curriculum vitae/resume) and documented training.

6.1.2 SOP Training

6.1.2.1 Records documenting training on specific procedures (SOPs) used for the manufacture of Tox product may not always exist because often the procedures have not yet been formalized.

6.1.2.2 When SOPs are available and applicable, production technicians should train on these SOPs and should document this training. See ***SOP 21600 - Training and Qualification of Personnel in a CGMP Environment.***

6.1.2.3 Personnel who are qualified and experienced with working in a BDP GMP environment are considered as qualified to work on GLP projects. However, these individuals must also train on any SOPs and other documents that are specific to the Tox project.

6.2 Buildings and Facilities

6.2.1 Manufacture Tox product in facilities that are clean and that minimize the potential for cross contamination.

6.2.2 Areas for manufacture of Tox product must be at least spatially separated from other areas within the laboratory during active production (to prevent cross-contamination and mixups).

6.2.2.1 Physical separation of activities may be appropriate to address safety issues.

6.2.2.2 If the manufacturing area is not already on a documented cleaning program, the area must be cleaned before its use for the manufacture of a Tox product. This must be documented. Include the cleaning agents used and their concentration, their lot numbers, expiration dates, date of cleaning, and the signature or initials of the technician performing the cleaning in the documentation.

6.3 Equipment

6.3.1 Quantitative process and test equipment must be calibrated and the calibration documented in accordance with ***SOP 21508 - Equipment Calibration Program***.

6.3.2 Equipment validation is not required.

6.3.3 Equipment is to be maintained in good working condition, be cleaned and prepared for use (as appropriate) using approved SOPs when available.

6.3.3.1 Use Equipment Logs to document these activities when available. Include in the cleaning documentation the cleaning agents used and their concentration, their lot numbers, expiration dates, date of cleaning, and the signature or initials of the technician performing the cleaning. Other equipment preparation documentation must include sufficient information to identify the piece of equipment, what was done, who did it, reagents and components used, etc.

6.4 Raw Materials

6.4.1 Materials used to manufacture Tox products are not required to be cleared or approved by BDP Materials Management/Inventory Control (MMIC). However, materials should be from the same supplier and of the same grade/catalog number that would be suitable for use in future Current Good Manufacturing Practice (CGMP) production.

6.4.1.1 Use of materials from current CGMP inventory is highly recommended.

6.4.2 Raw materials must be used within their expiration date, if one has been assigned.

6.4.3 When appropriate vials, stoppers, and crimps should be the same as the vials and stoppers that are anticipated to be used for the final GMP product.

6.4.4 Vials, stoppers, and crimps used in the manufacture of the Tox product must be washed (as appropriate) and sterilized according to existing BDP procedures. A record of these activities must be included with the production documentation of the Tox material.

6.4.5 For materials used, documentation must capture the material identification (including any "grade" designation), manufacturer's name, manufacturer's catalog number, manufacturer's lot number, BDP receiving number (if assigned) and manufacturer's expiration date (if provided).

6.4.6 Materials must be stored appropriately to protect their quality.

6.4.7 The preparation of buffers, reagents, etc., must be fully documented and include the lot/receiving number and expiration dates of components.

6.4.7.1 When possible, have final formulation buffers made by the GMP Buffer Preparation Group in Clinical Manufacturing.

6.4.7.2 If the buffer is a BDP final product and will be sent to a researcher for a toxicological study the part number and the lot number are to be assigned by BQA as per ***SOP 21405 - Assigning and Requesting Lot Numbers for Products***, and labeled as per ***SOP 21403 - Origination, Modification, and Control of Labels for GMP and GLP Products***.

6.5 Production and Process Controls

6.5.1 Establish a production plan and document it (preferably as a draft MPR). Preparation of this document helps in the planning of the production activities and prompts manufacturing technicians to capture sufficient information about the process.

6.5.1.1 When appropriate, use established SOPs to direct production activities and cite these SOPs in production documentation.

6.5.2 The Project Scientist and QA approve the production plan.

6.5.3 A formal lot number for the manufacture of Tox material must be obtained from the BQA Documentation Department. See ***SOP 21405 - Assigning and Requesting Lot Numbers for Products***.

6.5.4 The manufacturing area does not require a formal area clearance by BQA as a condition to start manufacture. The supervisor ensures that the equipment, area, etc., is clean and suitable for use.

6.5.5 Document production activities on the draft Batch Production Record (greatly preferred) or in a Laboratory Notebook.

6.5.5.1 If a laboratory notebook is used, it must capture the same information as noted in this section (6.0).

6.5.6 Verification of manufacturing activities by a second manufacturing person is not required.

6.5.7 In-process testing may be conducted by manufacturing and/or analytical (QC) personnel. Complete records of testing must be maintained (on a testing worksheet or in a Laboratory Notebook).

6.5.8 Filling of the Tox material into final vials must be performed in an ISO 5 (Class 100) area using aseptic technique. If a certified Biological Safety Cabinet is used, the room or area where the biological safety cabinet is located need not be classified or monitored.

6.5.9 Identify changes from the production plan or unexpected results and note them on the Batch Production Record (BPR) or in the Laboratory Notebook. Bring these to the attention of the Project Scientist. Although documentation of the change or unexpected result must be documented, they are not required to be logged into the GMP deviation system.

6.6 Packaging and Product Labeling

6.6.1 A label galley must be approved for use according to ***SOP 21403 - Origination, Modification and Control of Labels for GMP and GLP Products***.

6.6.2 Once labels are prepared for the labeling of a Tox product based on the approved label galley, they must be reviewed by BQA prior to use.

6.6.3 The area where labeling will occur does not require an area clearance by BQA as a condition to start labeling operations.

6.6.4 Labeling operations for Tox products do not require BQA observation.

6.6.5 Reconciliation of labels issued for use is required and must be documented.

6.7 Storage and Distribution

6.7.1 Tox material must be stored in calibrated storage units.

6.7.2 Quality Assurance releases Tox material according to ***SOP 21002 - Product Release***.

6.8 Laboratory Controls

6.8.1 At a minimum, perform tests for identity, strength, and purity whenever possible.

6.8.2 Submit testing requests for final release tests to QC according to ***SOP 22002 - Request for Quality Control Testing***.

6.8.2.1 As appropriate and mutually agreed upon by PA/QC, QA, and the Project Scientist, after accessioning the samples, PA/QC may return a portion of the sample to be tested back to the requesting department to have certain tests performed, e.g., potency or activity, when the requesting department has greater knowledge and experience performing the assay.

6.8.3 Final product tests for Tox material do not require method validation/qualification.

6.8.3.1 Final product tests require the use of appropriate positive and negative controls, standards, and suitability requirements, and must be properly documented.

6.8.4 Sterility testing of the Tox material is recommended. If sterility testing is not performed, then testing for extended microbial content is required.

6.9 Stability Testing

6.9.1 GLP regulations, 21 CFR 58.105 (b), require that the stability of each test or control article shall be determined before or concurrently with study initiation in accordance with established SOPs.

6.9.1.1 Stability has to be demonstrated for the duration of use of the article in the toxicological studies.

6.10 Documentation and Records

6.10.1 Documentation of the Production Plan

6.10.1.1 Master Production Records: Capture the plan for production (whenever possible) on at least a draft MPR. Use of this type of a document shows planning for the production process and prompts the production technician through the production activities and the data collection that is applicable.

- In the absence of a draft MPR, use a Laboratory Notebook to completely document production activities. ***See SOP 21408 - Laboratory Notebooks Control and Use***.

6.10.1.2 Standard Operating Procedures: Formal SOPs for production activities may not be available. However, production records need to capture WHAT was done in the production of a batch. Use of approved SOPs and worksheets is suggested whenever possible.

6.10.2 Documentation of the Execution of the Production Plan

6.10.2.1 Document execution of the production whenever possible on the draft BPR. If necessary, although not encouraged, a Laboratory Notebook may be used to document production.

6.10.2.2 Sufficient information must be captured to fully describe the production process, processing times, personnel, traceability of materials and equipment, suitability of equipment and areas, etc., so that the process can be duplicated at another time. Show calculations that are necessary and include units of measure.

6.10.3 Upon completion of a BPR or Laboratory Notebook documented project, the BDP Project/Manufacturing Supervisor reviews the document for technical accuracy and completeness. The Supervisor signs the document to indicate his/her review. The reviewed document is submitted to BQA for QA review.

6.10.4 BQA will review the Tox lot production records and QC test documentation according to ***SOP 21103 -*** *Quality Assurance Review of Completed Batch Production Records and Other Manufacturing Production Records*.

7.0 References & Related Documents

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

SOP 21405 *Assigning and Requesting Lot Numbers for Products*

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

SOP 21002 *Product Release*

SOP 22002 *Request for Quality Control Testing*

SOP 21408 *Laboratory Notebooks Control and Use*

SOP 21103 *Quality Assurance Review of Completed Batch Production Records and Other Manufacturing Production Records*

21 CFR 58.105 Test and Control Article Characterization

(a) The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented. Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility. In those cases where marketed products are used as control articles, such products will be characterized by their labeling.

(b) The stability of each test or control article shall be determined by the testing facility or by the sponsor either: (1) Before study initiation, or (2) concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch.

(c) Each storage container for a test or control article shall be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.

(d) For studies of more than 4 weeks' duration, reserve samples from each batch of test and control articles shall be retained for the period of time provided by §58.195.

21 CFR 58.107 Test and Control Article Handling

Procedures shall be established for a system for the handling of the test and control articles to ensure that:

(a) There is proper storage.

(b) Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.

(c) Proper identification is maintained throughout the distribution process.

(d) The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.

21 CFR 58.195 Retention of Records

(b) Except as provided in paragraph (c) of this section, documentation records, raw data, and specimens pertaining to a nonclinical laboratory study and required to be made by this part shall be retained in the archive(s) for whichever of the following periods is shortest: … (2) A period of at least 5 years following the date on which the results of the nonclinical laboratory study are submitted to the FDA in support of an application for a research or marketing permit. … (3) In other situations (e.g., where the nonclinical laboratory study does not result in the submission of the study in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.