Title: Establishing a BDP Quality Agreement with Subcontractors

SOP Number: 21108
Revision Number: 02
Supers edes: Revision 01
Effective Date: **DEC 19 2017**

Originator/Date: [redacted]

Approval/Date:

Approval/Date:

Table of Contents

1.0 Purpose

This Standard Operating Procedure (SOP) describes how a negotiated Quality Agreement is established with an individual subcontractor who will perform GMP/GLP work supporting BiopharmaceuticalDevelopment Program (BOP) projects.

2.0 Scope

This procedure applies to outsourced subcontracted activities supporting GMP/GLP projects.

3.0 Authority and Responsibility

3.1 The BOP Director of Quality Assurance and the Program and Technical Director are jointly responsible for indicating, "Quality Agreement required," as appropriate, on each Statement of Work issued for GLP/GMP-related subcontract activities.

3.2 The Leidos Biomedical Research, Inc. Research Subcontracts Representative is responsible for including the Quality Agreement Template with any requests for solicitation when the Statement of Work indicates that a Quality Agreement is required.

3.3 The BDP's Contracting Officer Technical Representative (COTR) is responsible for:

3.3.1 Assisting in the determination as to whether a Quality Agreement is needed for subcontractor activities.

3.3.2 Assisting in the negotiation of an individualized Quality Agreement with the subcontractor (when needed.)

3.3.3 Facilitating technical communication between the subcontractor and appropriate staff of the BDP.

3.4 The BDP Quality Assurance Director, or designee, is responsible for:

3.4.1 Determining whether a Quality Agreement is needed for subcontractor activities. See 3.1 above.

3.4.2 Negotiating an individualized Quality Agreement with the subcontractor, when necessary.

3.4.3 Approving the negotiated Quality Agreement.

3.4.4 Distributing the approved, negotiated Quality Agreement to involved parties. (See section 3.5.3).

3.5 The BDP Quality Assurance Department is responsible for:

3.5.1 Assigning a tracking number to customized, vendor-specific Quality Agreements.

3.5.2 Scanning the customized Quality Agreement onto the BDP Public Server.

3.5.3 Alerting appropriate BDP staff to the existence of the Quality Agreement.

3.5.4 Maintaining the original signed Quality Agreement on file.

4.0 Overview of the Process

4.1 The BDP of Leidos Biomedical Research, Inc. manufactures materials for clinical trials. The BDP may partner with other firms to perform some of the manufacture of these products. Subcontractors are solicited by the BDP based on knowledge of the subcontractor's capabilities and compliance status.

4.2 The BDP is committed to providing clinical products that possess the appropriate safety, identity, strength, quality and purity. The BDP is also responsible for the compliance of its selected subcontractors to applicable product and establishment standards as they relate to BDP-specific projects. As a result, auditing, access to the subcontractor's Quality System records, effective communication with the subcontractor, and a clear understanding of expectations, limitations, and responsibilities are critical to assuring appropriate safety, identity, strength, quality, and purity. It is in both parties' interest to collaborate to assure the consistent quality, integrity, purity and stability of the product. The Quality Agreement is negotiated with each project subcontractor and formalized to establish and document the

expectations that the BDP and the subcontractor have for each other when conducting the activities that support BDP projects.

4.3 Subcontractors performing GLP/GMP activities in support of BDP projects are provided a standard Quality Agreement Template prior to or at the time a solicitation is initially presented. The subcontractor may accept the provisions stated in the Quality Agreement Template or negotiate with BDP Quality Assurance to develop a modified Quality Agreement. The Quality Agreement is negotiated with each project subcontractor and formalized to establish and document the expectations that the BDP has for its subcontractors in performing manufacturing activities supporting BDP projects, prior to the award of the contract. In general, our expectation is that contractors design their systems and conduct activities in compliance with the Good Manufacturing Practice Regulations and Biological Standards appropriate for the manufacture of a clinical drug product, and that communication between the subcontractor and the BDP is timely and effective.

4.4 If a subcontractor requests that their Quality Agreement Template, rather than the BDP template, is used to start negotiations, then the templates should be compared and the best template selected to start negotiations.

5.0 References and Related Documents

5.1 During the development of a Statement of Work (SOW), the BDP Director of Quality Assurance and the Program and Technical Director, with assistance from the COTR, will make a decision regarding the need for a Quality Agreement with the subcontractor.

5.1.1 Work that supports GLP/GMP activities usually requires a Quality Agreement with the subcontractor.

5.2 The Leidos Biomedical Research, Inc. Research Contracts Representative prepares a formal document that describes the proposed work to be performed by the subcontractor. If this work has been identified as requiring a Quality Agreement, the Research Contracts Representative will include the Quality Agreement Template in the formal solicitation to the subcontractor.

5.3 As needed, the Quality Assurance Director, or designee, with assistance from the BDP COTR, will negotiate with the subcontractor to make changes/modifications to the Quality Agreement. Points for negotiation will be based on product impact, stage of product (GLP, GMP), capabilities of the subcontractor, alternate mechanisms that could provide acceptable control, etc. These decisions are documented and approved in a “customized” Quality Agreement with the subcontractor.

5.3.1 Customized Quality Agreements will be traceable to the vendor and the purchase request number from a tracking number that will appear in the footer of each page of the Quality Agreement. This tracking number will follow the convention:

5.3.2 *Vendor name (or vendor abbreviation)/Purchase request #/revision #.*

5.4 The BDP Quality Assurance Director, or designee, will arrange to have the customized Quality Agreement signed by the subcontractor’s Quality Contact. A signature from the Quality Contact of the BDP and the subcontractor are required to approve the Quality Agreement.

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

5.5 The original, signed Quality Agreement is forwarded to the BDP Quality Assurance Department.

5.5.1 The document is scanned.

5.5.2 The scanned file is named according to the tracking number at the footer of the document and electronically filed.

5.5.3 Appropriate BDP/Leidos Biomedical Research, Inc., staff is alerted (e-mail) to the existence of the completed Quality Agreement. Appropriate staff include at a minimum:

- BDP Director of Quality Assurance
- BDP Program and Technical Director
- BDP Program Manager
- BDP COTR
- Leidos Biomedical Research Contracts Representative
- BDP Quality Assurance Audit Manager.

5.5.4 The original document is filed.

6.0 Revising Existing Quality Agreement

6.1 Existing Quality Agreements may be revised at any time by following steps 3.3 through 3.5, above. The tracking number in the document footer must be updated to reflect a new revision level.

7.0 Record

7.1 Original Quality Agreements are filed in the Quality Assurance Department.

7.2 Records are maintained per ***SOP 21407 – Records Retention*.**

8.0 Attachments

8.1 Quality Agreement

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

Attachment 1

QUALITY AGREEMENT

Purchase Request # _____
Contract # (when available) _____
Revision: SOP 21108 Rev 02(12/19/17)
Supersedes: None

BETWEEN:

Leidos Biomedical Research, Inc.
NCI Frederick
PO Box B
Frederick, MD 21702-1201

Approved By Leidos Quality Contact: _____
Printed Name: _____
Title: _____
Date: _____

AND

SUBCONTRACTOR
Company Name (Insert)
Address (Insert)
Address (Insert)

Approved By Subcontractor Quality Contact: _____
Printed Name: _____
Title: _____
Date: _____

Leidos Biomedical Research, Inc., CONTACTS

Primary Contact Quality Assurance
INSERT

Contracting Officer's Technical Representative (COTR)
INSERT

Business Contact
INSERT

Person(s) in the Plant Contact
INSERT

SUBCONTRACTOR CONTACTS

Primary Contact
INSERT

Quality Assurance Contact
INSERT

Business Contact
INSERT

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

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

TABLE OF CONTENTS

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

1. QUALITY AGREEMENT

1.1 This document establishes the expectations that Leidos Biomedical Research, Inc., has for its SUBCONTRACTORS in performing manufacturing activities supporting Leidos Biomedical Research, Inc., projects.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

1.1.1 The SUBCONTRACTOR must design systems and conduct activities in compliance with various laws and regulations including, but not limited to:

- State and local laws/regulations/ ordinances/ standards, etc.
- 21 CFR 210 / 211: Good Manufacturing Practice Regulations
- 21 CFR 600, 601, 610: Biologics regulations
- 21 CFR 11, Electronic Records and Signature regulations

1.1.2 Special attention is required to design systems and conduct activities to prevent cross contamination of product and to generate documentation that assures the traceability of equipment, materials, personnel, products, processes, etc., in accordance with FDA/ICH Guidance Documents.

1.2 Documentation and records pertaining to Leidos Biomedical Research, Inc., product, processes or supporting activities must be made available to Leidos Biomedical Research, Inc., when requested for review. Copies must be provided when requested.

1.3 Leidos Biomedical Research, Inc., and the SUBCONTRACTOR will collaborate on overall product performance to assure the consistent and acceptable quality, integrity, purity and stability of the product.

2. TERM OF AGREEMENT

2.1 This agreement will be effective at the time all required signatures are captured on this document. The Quality Agreement shall be completed and approved by both parties prior to the execution of the subcontract or Basic Ordering Agreement. The Quality Agreement shall be made an attachment to or referenced by the Subcontract or Basic Ordering Agreement.

2.1.1 After the close of the contract, the SUBCONTRACTOR agrees to provide documents, testing, record review, as needed, to investigate issues of product quality.

2.1.2 After the close of the contract, the SUBCONTRACTOR agrees to notify Leidos Biomedical Research, Inc., of any issue that they become aware of that could adversely affect the quality of the product produced. These events include, but are not limited to, failure of validations or calibrations that affect Leidos Biomedical Research, Inc.'s product, or subsequently detected error, deficiencies or inconsistencies with manufacturing or test records.

2.2 Changes to this document may be made as needed with the written approval of both parties. The document will be modified, re-approved and re-signed.

3. PRODUCT

3.1 The product and a description of activities applicable to this agreement are described in its associated technical specification and/or protocol, and subcontract referenced on the cover page of this document.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

4. COMMUNICATION

4.1 Names and information for Leidos Biomedical Research, Inc., and the SUBCONTRACTOR contacts are stated on the cover page of this document.

4.2 Each party will notify the other party's Primary Contact and QA Contact immediately (within 1 business day) of any issues that impact the SUBCONTRACTOR's ability to conduct Leidos Biomedical Research, Inc.,-contracted activities.

4.3 Events that require notification by the SUBCONTRACTOR to Leidos Biomedical Research, Inc., include, but are not limited to, the events listed below. The SUBCONTRACTOR should also alert Leidos Biomedical Research, Inc., of any other issues or information that have (or could have) an effect on the quality of Leidos Biomedical Research, Inc., projects. Communication may occur via phone, FAX, or electronic mail. All communications that do not generate a written record (i.e., phone communications or communication at a meeting, etc.) must be followed with a written notification within 2 business days.

REQUIRED NOTIFICATION BY THE SUBCONTRACTOR TO Leidos Biomedical Research, Inc.		
EVENT	Notification required to Leidos Biomedical Research, Inc.'s ….	Timeframe
Changes to critical staff	Technical and QA Contacts	3 business days
Events that would impact the SUBCONTRACTOR's ability to conduct Leidos Biomedical Research, Inc.-contracted activities	Technical and QA Contacts	Within 1 business day
Discussion of technical issues	Technical Representative	As needed
Discussion of quality issues	QA Contact	As needed
Request for the convening of a Quality Review Board	QA Contact	As needed
Need anticipated for reprocessing / rework	Technical/QA/ Business Contacts	Before reprocessing / rework
Verified OOS event	Technical and QA Contacts	Within 1 business day
Errors or deviations	Technical/QA/ Business Contacts	Within 1 business day

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

REQUIRED NOTIFICATION BY THE SUBCONTRACTOR TO Leidos Biomedical Research, Inc.		
EVENT	Notification required to Leidos Biomedical Research, Inc.'s ….	Timeframe
Product disposition issues	Technical/ QA/ Business Contacts	When recognized
Anticipation of rejecting a batch	Technical/ QA/ Business Contacts	Before the decision to reject
Initiation of an FDA (or other regulatory) inspection during the manufacture of a Leidos Biomedical Research, Inc., product.	QA Contact	Within 1 business day
Receipt of an FDA 483, Warning Letter or other regulatory action	QA Contact	Immediately (within 1 business day)
Destruction of contract-associated records	QA Contact	At least 30 days prior to record destruction

4.4 Events that require notification by Leidos Biomedical Research, Inc., to the SUBCONTRACTOR include, but are not limited to, the events that are listed below. Leidos Biomedical Research, Inc., will also alert the SUBCONTRACTOR of any other issues or information that have (or could have) an effect on the quality of Leidos Biomedical Research, Inc., projects. Communication may occur via phone, FAX, or electronic mail. All communications that do not generate a written record (i.e., phone communications or communication at a meeting, etc.) must be followed with a written notification within 2 business days.

REQUIRED NOTIFICATION BY Leidos Biomedical Research, Inc., TO THE SUBCONTRACTOR		
EVENT	Notification required to the SUBCONTRACTOR's ….	Timeframe
Events that would impact the SUBCONTRACTOR's ability to conduct Leidos Biomedical Research, Inc.-contracted activities	Technical/QA/ Business Contacts	Within 1 business day)

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

Request for the convening of a Quality Review Board	QA Contact	As needed
Deviations or Errors detected by Leidos Biomedical Research, Inc., during review	QA Contact	As discovered
Determination that a batch is unacceptable for release	QA / Business Contact	As discovered

5. ADMINISTRATIVE INFORMATION

5.1 Organizational Structure

SUBCONTRACTORs must maintain an adequate number of qualified personnel to perform and supervise Leidos Biomedical Research, Inc., project-related activities and to meet the appropriate cGMP regulations and regulatory guidelines.

5.1.1 Personnel must have the appropriate education and experience and be adequately trained on all procedures applicable to their responsibilities for the manufacture of Leidos Biomedical Research, Inc., products. This training must be in a formal training program that delineates requirements for basic and on-the-job training based on job function. In addition, there must be a requirement for mandatory cGMP training for new employees and refresher training conducted at a sufficient frequency to ensure employees remain familiar with requirements as they apply to their day-to-day responsibilities. This training must be documented and available for review.

5.1.2 Changes to Key Personnel relating to the performance of this subcontract must be conducted pursuant to Section G. “Key Personnel” of the Subcontract.

5.2 Quality Review Board

5.2.1 A Quality Review Board will be established, whenever needed, consisting of the designated contacts of Leidos Biomedical Research, Inc., and of the SUBCONTRACTOR and including, as necessary, other appropriate members from each organization. The Quality contacts from each organization will serve as co-chairs of this forum.

5.2.2 The Quality Review Board will meet as needed to provide appropriate quality oversight of the project and will serve as the mechanism for resolving quality matters.

5.2.3 The QA or Primary Contact of either organization can request convening the Quality Review Board.

6. LEIDOS BIOMEDICAL RESEARCH, INC., RESPONSIBILITIES

6.1 Technology Transfer Information

6.1.1 Leidos Biomedical Research, Inc., will provide available technology transfer documents that pertain to the work the SUBCONTRACTOR will be

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

performing. When available, these may include (but are not limited to) production and test methods, sampling plans, sample handling instructions, specifications, safety information, etc.

6.1.2 Leidos Biomedical Research, Inc., will provide the information needed to format specific product labels.

6.1.3 Leidos Biomedical Research, Inc., will provide reference standards where applicable.

6.1.4 Leidos Biomedical Research, Inc., will be responsible for establishing and approving any required stability program.

6.2 Participation in Planning for Manufacture

6.2.1 Leidos Biomedical Research, Inc., will provide Quality Assurance review and approval of all relevant process-specific procedures including (but not limited to) standard operating procedures, master production and control records, quality control test methods, specifications, etc.

6.2.2 Leidos Biomedical Research, Inc.'s COTR is available to the SUBCONTRACTOR to discuss technical issues or recommend changes. As needed, the COTR may ask other Leidos Biomedical Research, Inc., qualified staff to participate in technical discussions. Any changes or deviations to the Statement of Work must go through the Leidos Biomedical Research, Inc., Contracting Officer for modification and official approval.

6.2.3 Leidos Biomedical Research, Inc.'s QA Contact is available to the SUBCONTRACTOR to discuss quality or regulatory issues. As needed, the QA Contact may ask other Leidos Biomedical Research, Inc., qualified staff to participate in these discussions.

6.2.4 The Quality Review Board may be convened at any time at the request of the SUBCONTRACTOR and / or Leidos Biomedical Research, Inc., to discuss issues or to plan for future activities.

6.3 Manufacturing Oversight

6.3.1 Leidos Biomedical Research, Inc., will verify through batch record review and test record review that all clinical trial material complies with predetermined specifications and has been released to Leidos Biomedical Research, Inc., by the SUBCONTRACTOR's QA Department.

6.3.2 Leidos Biomedical Research, Inc., will assist in the evaluation of errors, deviations and out-of-specification events.

6.3.3 Leidos Biomedical Research, Inc., will notify the SUBCONTRACTOR of any deviations or errors detected during a review of project-specific documentation. The SUBCONTRACTOR will subsequently document these events according to its established deviation procedure.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

6.3.4 In the event Leidos Biomedical Research, Inc., finds a batch unacceptable for release, Leidos Biomedical Research, Inc., will notify the SUBCONTRACTOR's QA Contact and discuss the reasons for the rejection. A meeting of the Quality Review Board may be convened to discuss these issues.

6.4 Product Release to the Clinic

6.4.1 The SUBCONTRACTOR does not release the final product to the clinic for use in humans. Final product may only be released by Leidos Biomedical Research, Inc., Quality Assurance Department for use in humans.

7. MANUFACTURING AND LOGISTICS

7.1 Person-in-the-Plant

7.1.1 The SUBCONTRACTOR must allow Leidos Biomedical Research, Inc.'s Person-in-the-Plant (PIP) access to the facility to observe various operations and assist in problem solving for the activities specific to Leidos Biomedical Research, Inc., project(s). Any such "in plant visits" will be coordinated in advance by both parties.

7.1.2 The SUBCONTRACTOR must allow Leidos Biomedical Research, Inc.'s Person-in-the-Plant and QA personnel to verify that all documentation and records are complete and accurate, including, but not limited to, that raw materials and components are released, equipment is within calibration, and the final training specific to the Leidos Biomedical Research, Inc.'s clinical supply manufacturing and testing efforts has occurred with appropriate manufacturing personnel. This may also be performed by Leidos Biomedical Research, Inc.'s QA during batch record review.

7.1.3 The SUBCONTRACTOR must provide training to the Person-in-the-Plant as needed to comply with any specialized gowning or safety requirements.

7.2 Facilities, Utilities and Equipment

7.2.1 General

7.2.1.1 Facilities, utilities and equipment must be qualified/validated as is appropriate for the work being performed.

7.2.1.2 Equipment, facilities or utilities that support the aseptic filling process must be fully validated.

7.2.1.3 The SUBCONTRACTOR must have and maintain a preventive maintenance program for all critical systems, utilities, manufacturing and QC instrumentation and equipment. The documentation requirements must include a record of the type, frequency, and details of service checks. The preventive maintenance program includes verification that the monitoring system alarms and the back-up generator, if so equipped, are functioning properly.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

7.2.2 Facilities and Utilities

7.2.2.1 All utilities that could impact product quality (WFI, purified water, steam, gases, compressed air, and HVAC) are qualified and appropriately monitored. Action is taken when limits are exceeded.

7.2.2.1.1 The SUBCONTRACTOR will have and maintain a HEPA filter test and certification program for filters located in LFBSCs and classified areas.

7.2.2.2 The SUBCONTRACTOR must have and maintain procedures for ensuring that in-process and final product, personnel, raw materials, equipment and waste flows are controlled to prevent cross contamination.

7.2.2.3 The SUBCONTRACTOR must have and maintain a procedure for area clearance and changeover between product campaigns.

7.2.2.4 The SUBCONTRACTOR will assure that access to the manufacturing and testing facilities are restricted to authorized personnel. Authorized visitors must be escorted at all times in areas used to manufacture, test and store Leidos Biomedical Research, Inc., product.

7.2.3 Equipment

7.2.3.1 The SUBCONTRACTOR must have and maintain a calibration program. In the event an instrument is found to be out-of-tolerance (OOT), the period in which the instrument was in use starting with the last successful calibration will be evaluated for product impact.

7.2.3.2 The SUBCONTRACTOR will maintain records of equipment usage, cleaning, testing, maintenance, and calibration performed.

7.2.3.3 The SUBCONTRACTOR will provide information to Leidos Biomedical Research, Inc., describing how manufacturing equipment was used immediately prior to its use in the manufacture of Leidos Biomedical Research, Inc.'s product, how the equipment was cleaned to prevent carryover of the previous product, and test results that document that the equipment was adequately cleaned and suitable for use in the production of Leidos Biomedical Research, Inc., product.

7.2.3.4 The SUBCONTRACTOR will use disposable or dedicated equipment whenever possible during the manufacture of Leidos Biomedical Research, Inc.'s product.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

7.3 Environment

7.3 1 The SUBCONTRACTOR must have and maintain programs for environmental monitoring for viable surface and air samples, non-viable air particulate samples, personnel monitoring, water (WFI, clean steam and purified water), and gases that includes scheduled testing, reporting and trending of results, alert and action levels based on historical data and regulatory requirements, and an investigation procedure for excursions.

7.3.2 The SUBCONTRACTOR must have and maintain a procedure that specifies personnel gowning requirements based on room classification and use. There must be a gowning qualification and certification program for personnel performing aseptic operations that include routine testing and data trending.

7.4 Cleaning and Disinfection

7.4.1 The SUBCONTRACTOR must utilize dedicated product contact equipment and parts that have not been previously used for other products whenever possible when manufacturing Leidos Biomedical Research, Inc., product.

7.4.2 The SUBCONTRACTOR must have and maintain written Leidos Biomedical Research, Inc., approved procedures for cleaning product dedicated equipment that reduces lot-to-lot carryover, eliminates endotoxin and microbial contamination, and removes the residual cleaning agent(s).

7.4.3 The SUBCONTRACTOR must have and maintain cleaning validation for non-dedicated, product contact equipment, e.g., pump heads, bioreactors, fermentors, chromatography columns, etc., that demonstrates adequate removal of the previous product. Leidos Biomedical Research, Inc, QA personnel shall review the SUBCONTRACTOR's plan and documentation relating to the cleaning and prevention of cross-contamination of non-dedicated product contact equipment to be used for the manufacture of Leidos Biomedical Research, Inc., products prior to the start of the manufacturing campaign.

7.4.4 The SUBCONTRACTOR must have and maintain a procedure for facility cleaning based on room classification and use, including responsibilities, schedules, a list of qualified disinfectants, and documentation requirements.

7.4.5 The SUBCONTRACTOR must have conducted a disinfectant effectiveness study that demonstrates that their approved disinfectants have been qualified to effectively reduce levels of indigent microbial contamination and viruses from surfaces within the facility.

7.5 Computerized Processes

7.5.1 The SUBCONTRACTOR must have and maintain procedures for the operation and maintenance of computerized systems.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

7.5.1.1 These procedures will include a disaster recovery plan that ensures that data integrity is maintained for all computerized systems in the event of a system failure that results in a permanent loss of electronic records.

7.5.2 The SUBCONTRACTOR will assure that the computerized systems used in the production or support of GMP activities have been appropriately qualified based on the intended use of the material and based on the application's diversity, complexity and criticality.

7.5.3 The SUBCONTRACTOR will assure that computerized systems are compliant with 21 CFR Part 11 and have sufficient controls to prevent unauthorized access or changes to the data and to prevent omissions in data. In addition, an audit trail will be maintained that records the original data, any change to the original data, who made the change and when the data was changed. Where critical data are being entered manually, there is an additional check on the accuracy of the data. This can be done by a second operator or by the system itself.

7.6 Raw Materials, Components, Component Closures, In-process Intermediates, Finished Products

7.6.1 The SUBCONTRACTOR must have and maintain a written, approved procedure for the receipt, inspection, handling, sampling, testing, approval or rejection, and disposition of raw materials, components and component closures, in-process intermediates and finished product.

7.6.2 The SUBCONTRACTOR must have and maintain a procedure for proper segregation, storage, and controlled distribution of raw materials, components and component closures, and in-process intermediates to ensure traceability, and prevent cross contamination or the accidental use of unreleased materials.

7.6.3 The SUBCONTRACTOR must have and maintain a procedure that requires the identification of all animal derived raw materials and provide documented proof of the country of origin. Raw materials of animal origin should be avoided. Use of any material of animal origin must be discussed with the Leidos Biomedical Research, Inc., COTR and Quality Contact prior to use.

7.6.4 The SUBCONTRACTOR must maintain relevant Certificates of Analysis, Certificates of Compliance and/or Certification of Origin (as appropriate) for raw materials.

7.7 Product and Lot Numbers

7.7.1 The SUBCONTRACTOR must have and maintain a written, approved procedure for the issuance of part and lot numbers that are used in cGMP documentation so that materials are uniquely identified and traceable.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

7.8 Dates of Manufacture and Expiration

7.8.1 The date of manufacture for the final product fill is defined as the date of the final sterile filtration.

7.8.2 The shelf life of the final product will be supported by stability studies. The stability studies may be conducted by the SUBCONTRACTOR or Leidos Biomedical Research, Inc., as indicated in the contract.

7.8.3 The SUBCONTRACTOR and Leidos Biomedical Research, Inc., will work together to establish any necessary expiration dates for raw material, intermediate products, solutions, etc.

7.9 Reprocessing / Rework

7.9.1 The SUBCONTRACTOR must contact the Leidos Biomedical Research, Inc., COTR, the Leidos Biomedical Research, Inc., QA Contact, and the Contract's contact before initiating reprocessing or rework on any material. A meeting of the Quality Review Board will usually be convened to discuss these issues.

7.10 Product Labeling and Packaging

7.10.1 Labeling and packaging operations must be designed to provide label and component accountability and reconciliation.

7.10.2 The SUBCONTRACTOR will generate a label galley or proof for review and approval by Leidos Biomedical Research, Inc. This review and approval by Leidos Biomedical Research, Inc., must be documented.

7.10.3 The SUBCONTRACTOR must generate the labeling required to label the product according to the approved label proof. This labeling must be reviewed and approved according to the SUBCONTRACTOR's written procedures before the labeling is issued for use.

7.10.4 The SUBCONTRACTOR must have and maintain written, approved procedures for the control of labels and labeling materials, including the approval, issuance, use and reconciliation and disposal of unused labels.

7.11 Storage and Shipment of Product

7.11.1 The SUBCONTRACTOR will assure that product is stored in suitable storage facilities that protect the product from possible deterioration, interference, theft, cross contamination, intermixing with other materials, or accidental use of unreleased material.

7.11.2 The SUBCONTRACTOR will package Leidos Biomedical Research, Inc., product for transit as described in the contract. Each shipment will include a temperature-monitoring device unless appropriate shipping validation studies have been conducted and approved by Leidos Biomedical Research, Inc. These records will become part of the product's batch production and control record.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

8. QUALITY CONTROL

8.1 General

8.1.1 No additional testing or any change to testing specifications may occur without approval by the Leidos Biomedical Research, Inc., COTR, the QA contact, and the Contract's contact; and the completion of any required change control documentation.

8.2 Test Specifications

8.2.1 The release testing specified for this project must be captured in a master specification document that is approved by Leidos Biomedical Research, Inc., COTR and QA contact.

8.3 Test Method Qualification

8.3.1 The SUBCONTRACTOR will assure that compendial test methods are qualified and that product-specific analytical methods have at least an approved test method using, as indicated, controlled reference standards, positive & negative controls, and/or system suitability checks.

8.3.2 Non-compendial methods must be qualified/validated.

8.4 Test Execution

8.4.1 Routine testing must be conducted according to written procedures. Non-routine and Leidos Biomedical Research, Inc., product specific testing must be performed according to written and jointly approved testing procedures.

8.5 Evaluation of Test Results

8.5.1 The SUBCONTRACTOR will evaluate test results to confirm conformance to established specifications.

8.5.1.1 The results of testing by SUBCONTRACTORs must be reviewed and approved by the SUBCONTRACTOR's Quality Assurance Contact to confirm that the test results have been reviewed and approved and meet the specified testing requirements.

8.5.2 The SUBCONTRACTOR will establish a procedure for documenting deviations and the investigation of OOS test results.

8.5.3 The SUBCONTRACTOR must immediately initiate an OOS investigation for any product testing performed by the SUBCONTRACTOR that produces a test result that fails to meet a specification or action limit. This investigation must be documented.

8.5.3.1 The SUBCONTRACTOR must immediately notify the Leidos Biomedical Research, Inc., COTR and Quality Contact when an OOS event occurs.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

8.6 QC Materials

8.6.1 QC materials must be received according to the SUBCONTRACTOR's receivable policies for GMP raw materials.

8.6.2 Qualification of critical quality control materials will be performed according to written and jointly approved specifications.

8.7 Reserve and Retention Samples

8.7.1 The holding of reserve or retention samples will be specified in the contract. Samples must be held in storage conditions that protect the sample's purity, identity, safety, sterility and quality. Holding areas must be regularly monitored for conformance to environmental requirements.

8.8 Stability Program

8.8.1 The SUBCONTRACTOR will execute any stability testing required by the contract and will comply with GMP requirements for Laboratory Controls for this testing.

9. QUALITY ASSURANCE

9.1 Documentation

9.1.1 Master Production and Control Records and Product-Specific SOPs

9.1.1.1 The SUBCONTRACTOR is responsible for generating product-specific manufacturing and testing documentation designed to direct the production of product that is compliant with GMP requirements and to capture appropriate process data.

9.1.1.2 The SUBCONTRACTOR and Leidos Biomedical Research, Inc., shall jointly approve these documents before the commencement of manufacturing.

9.1.1.3 The SUBCONTRACTOR shall provide copies to Leidos Biomedical Research, Inc.'s QA Contact of all project-specific documents that have been approved by the Leidos Biomedical Research, Inc.

9.1.2 General SOPs

9.1.2.1 The SUBCONTRACTOR's QA is responsible for generating and maintaining all SOPs and other documentation supporting cGMP operations within its facility. Leidos Biomedical Research, Inc., representatives must be permitted to review these documents on request. Leidos Biomedical Research, Inc., personnel will not review documentation specific to non-Leidos Biomedical Research, Inc., products.

9.1.3 Record Retention

9.1.3.1 The SUBCONTRACTOR will retain all manufacturing master production and control records, batch production and control

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

records, production procedures, testing documentation, and shipping records in accordance with its internal record retention requirements and in compliance with 21 CFR 211.180d.

9.1.3.2 At least thirty days prior to record destruction, the SUBCONTRACTOR shall alert the Leidos Biomedical Research, Inc., Quality contact. Leidos Biomedical Research, Inc., may request that the documentation or portions of the documentation be forwarded to Leidos Biomedical Research, Inc., for archiving. The SUBCONTRACTOR shall not destroy Leidos Biomedical Research, Inc., related documentation without written approval from Leidos Biomedical Research, Inc.

9.2 Deviations and Investigations

9.2.1 The SUBCONTRACTOR QA must establish a corrective/preventive action (CAPA) system compliant with the requirements of CGMPs.

9.2.2 As part of the investigation into a failure, error, or deviation, the SUBCONTRACTOR must assess the event's impact on the affected product's purity, potency, integrity, safety, and quality. The Leidos Biomedical Research, Inc., COTR and Quality Contact shall assist in this evaluation.

9.2.3 The SUBCONTRACTOR is responsible for alerting Leidos Biomedical Research, Inc., of any failures, errors, or deviation events. This notification must be made immediately and within the next business day of discovery.

9.2.4 Corrective and preventive actions must be completed within 30 days from recognizing the event. If the completion of these actions requires more than 30 days, interim status reports must be filed at 30 days and regularly thereafter until the actions are closed.

9.2.5 Planned deviations and changes that could possibly impact the manufacture and testing of Leidos Biomedical Research, Inc., products may not be executed without being appropriately reviewed and approved by the Leidos Biomedical Research, Inc., COTR and Quality Contact.

9.2.6 The SUBCONTRACTOR must have a procedure for handling complaints that requires as part of the investigation an immediate assessment of batch records, test records, supporting documentation, and if applicable, stability data.

9.2.6.1 The SUBCONTRACTOR shall notify Leidos Biomedical Research, Inc., COTR and Quality Contact within one business day of any complaints related to Leidos Biomedical Research, Inc., product.

9.3 Right to Audit

9.3.1 SUBCONTRACTORs should be prepared to host audits by Leidos Biomedical Research, Inc., at least annually. Leidos Biomedical Research,

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

Inc., will provide the SUBCONTRACTOR sufficient notice of the intent to audit or inspect the facility, manufacturing operations or testing operations for compliance with cGMPs and with the Quality Agreement. Audit duration is typically 2 days.

9.3.1.1 Audits will be scheduled with a minimum of a 2-week lead time with a maximum of 4 weeks from the initial request with the exception of "for cause" audits.

9.3.1.2 For Cause Audits: Scheduling of a "for cause" audit is determined on a case-by-case basis and can occur within 48 hours of the identification of a problem.

9.3.1.3 Leidos Biomedical Research, Inc., will coordinate the scheduling of audits with the SUBCONTRACTOR's management so that appropriate staff is available for the audit. Leidos Biomedical Research, Inc.'s audit team may include Leidos Biomedical Research, Inc., staff, government employees, and/or consultants employed by Leidos Biomedical Research, Inc.

9.3.2 At the conclusion of the audit, an exit meeting shall be held with representatives from Leidos Biomedical Research, Inc., and the SUBCONTRACTOR to discuss significant audit findings. A written audit report will be provided to the SUBCONTRACTOR, typically within 30 days of the conclusion of the audit.

9.3.3 The SUBCONTRACTOR shall respond to audit observations within 30 days and detail the necessary corrective actions and timeframes for correction. Alternately, Leidos Biomedical Research, Inc., may provide a proposed corrective/preventive action plan to the SUBCONTRACTOR that identifies system deficiencies and recommended corrective actions and timelines for completions.

9.3.4 The SUBCONTRACTOR shall provide periodic reports (not less than every 6 months) on the progress of any corrective actions that require an extended period to implement.

9.4 Change Management

9.4.1 The SUBCONTRACTOR must have a written, approved procedure for managing and tracking changes to master production and control records, bill of materials, analytical standards, test methods (for raw materials and product), raw material and product specifications and changes to validated facilities, utilities, computer systems, equipment or processes used in the cleaning, manufacturing, testing, storage or shipment of Leidos Biomedical Research, Inc., product. This procedure must require a documented technical and GMP impact assessment for all changes.

9.4.2 Proposed changes to project-specific documentation may only be accepted with the written approval of Leidos Biomedical Research, Inc., and may require validation before the change may be implemented.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

9.5 Document Distribution

9.5.1 The SUBCONTRACTOR will provide copies to the Leidos Biomedical Research, Inc., QA Contact of all project-specific documents that have been approved by Leidos Biomedical Research, Inc.

9.6 Disposition of Product (Batch Release or Rejection)

9.6.1 Manufacturer's Release

9.6.1.1 The SUBCONTRACTOR's Quality Assurance must review all batch production and test records including label reconciliation, environmental monitoring data and trends, deviations and investigations. The SUBCONTRACTOR'S QA must confirm that the process was executed according to established requirements and that any deviations, etc., have been satisfactorily identified (documented) and addressed.

9.6.1.1.1 The SUBCONTRACTOR has the authority to reject batches, however, the SUBCONTRACTOR will notify Leidos Biomedical Research, Inc.'s Technical and QA Contact of any batch being considered for rejection prior to the decision for rejection. A meeting of the Quality Review Board will usually be convened to discuss this issue and explore possible courses of action.

9.6.1.2 The SUBCONTRACTOR must provide a Certificate of Analysis to Leidos Biomedical Research, Inc., which includes:

- Name and address of manufacturer
- Name of product (or product description)
- Batch or lot number
- Date of manufacture
- Quantity (# units and unit volume) available for the clinic
- Expiration date or re-test date based on stability data (if applicable)
- A list of each test performed, method description, specification and result
- Review and approval signatures (Manufacturing or QC) and QA

9.6.1.3 The SUBCONTRACTOR must provide a Certificate of Conformance to Leidos Biomedical Research, Inc., that verifies that the product was manufactured in compliance to cGMP regulations.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

9.6.1.4 The SUBCONTRACTOR must provide a copy of the batch production and control record and all supporting documents including, but not limited to:

- QA reviewed and signed batch production and control record and buffer preparation records.
- All raw data and final reports for in-process and release tests, including all associated OOS reports
- Certificates of Analysis, and Certificates of Origin (or source origin statements), when applicable, for all raw materials, components and component closures
- Environmental and personnel monitoring data and/or trends
- Sterilization and depyrogenation records
- Label issuance and reconciliation records
- Filter integrity test results for sterilizing filters
- Transaction history (inventory at date of manufacture and all changes in inventory subsequent to that date) for bulk drug substance and/or finished drug product.
- Product storage monitoring data
- Copy of any other documentation of any communication between Leidos Biomedical Research, Inc., and the SUBCONTRACTOR that have affected the manufacture or testing of the product.

9.6.2 Product Release to the Clinic

9.6.2.1 The SUBCONTRACTOR does not release the final product to the clinic for human use. Final product may only be released by Leidos Biomedical Research, Inc Quality Assurance Department for use in humans.

10. REGULATORY COMPLIANCE

10.1 Regulatory Documentation

10.1.1 The SUBCONTRACTOR agrees to provide to Leidos Biomedical Research, Inc.'s Technical and Quality Contacts all documentation required for regulatory submissions and requests by Regulatory agencies. This may include items such as the Chemistry Manufacturing Control (CMC) section information to support an IND application, technical bulletins, summary reports, batch production and control records, Certificates of Analysis, source/origin information on raw materials or testing documentation.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

10.2 Regulatory Inspections and Correspondence

10.2.1 The SUBCONTRACTOR must notify the Leidos Biomedical Research, Inc., QA Contact immediately (within 1 business day) when an FDA (or other regulatory agency) inspection is commencing during the manufacture of a Leidos Biomedical Research, Inc.'s product.

10.2.2 For inspections that involve Leidos Biomedical Research, Inc., product, the SUBCONTRACTOR shall allow a representative of Leidos Biomedical Research, Inc., to be present.

10.2.3 The SUBCONTRACTOR must notify the Leidos Biomedical Research, Inc., QA Contact, immediately (within 1 business day) on the receipt of an FDA 483, Warning Letter, or other regulatory action from FDA (or similar communication from other regulatory agencies).

10.2.4 Commitments to regulatory agencies regarding Leidos Biomedical Research, Inc., product must only be made after agreement has been reached between Leidos Biomedical Research, Inc., and the SUBCONTRACTOR. A meeting of the Quality Review Board will likely be convened to discuss this issue and to develop a mutually agreed-upon course of action.

10.3 Drug or Biologics Master File

10.3.1 If applicable, the SUBCONTRACTOR will provide a letter of authorization to reference the SUBCONTRACTOR's Drug or Biologics Master File.

11. RESOLUTION OF QUALITY-RELATED ISSUES

11.1 Quality-related issues will be discussed at the Quality Review Board where all parties shall strive to reach an agreement.

12. VALIDATION / VERIFICATION

12.1 Validation Master Plan

12.1.1 The SUBCONTRACTOR shall have and maintain a Validation Master Plan that identifies critical equipment, systems and processes used to manufacture, test and evaluate product, and the requirements for validation and revalidation.

12.2 Process Validation

12.2.1 The SUBCONTRACTOR will establish and implement a procedure for the development and execution of Leidos Biomedical Research, Inc., specific Process Validation (PV) Test Plans as indicated in the manufacturing contract that appropriately identify critical process parameters to be controlled and monitored. Once validated, changes to critical process parameters will be implemented through a formal change control program that requires Leidos Biomedical Research, Inc., pre-approval.

12.2.2 The SUBCONTRACTOR is responsible for assuring that the sterile fill process into final containers is fully validated, documented, and approved.

QUALITY AGREEMENT

Reference: SOP 21108 Rev 02

The SUBCONTRACTOR must allow Leidos Biomedical Research, Inc., representatives to review protocols and final reports associated with Leidos Biomedical Research, Inc., specific projects.

12.3 Cleaning Verification/Validation

12.3.1 The SUBCONTRACTOR is responsible for assuring that residues from previous uses of the equipment have been removed to acceptable levels. This verification activity must be documented. The SUBCONTRACTOR shall allow Leidos Biomedical Research, Inc., QA personnel to review process residuals removal qualifications and test results.

12.4 Cleaning and Disinfection Validation

12.4.1 See previous section "Manufacturing and Logistics," subsection "Cleaning and Disinfection".